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PAIN MANAGEMENT SUMMIT
Focus on Opioid Therapy

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AGENDA

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Meeting Objectives

MATTHEW WIEMAN, MD: Welcome to the Pain Summit. Thanks for coming today. I think we all can see across the tables that we really have a great group of folks here today. So, welcome to Philadelphia. Some of you are already here. Some of you took a little bit longer to get here than others, but I appreciate the effort. Today is going to be a really solid day just based on some of the brief discussions we even had last night.

Real briefly, the housekeeping. Bathrooms past the elevators over to the side. If you could just check your phones of course, make sure those are in a silent mode, and if there's anything that you guys need about meeting logistics, the CHC team on this side of the wall here will be able to help you out with that.

The meeting today is supposed to not be at all about didactic teaching. It's really going to be very short discussions based on the slides, and then opening it up to the whole group for your opinions, because that's what we're here for, not to talk about some of the bullets on a slide. We're here to get opinions on what you folks feel will help us better create or optimize the life cycle plan and the path forward clinically for oxymorphone and Opana ER specifically.

So we'll talk about a lot of different specifics, but it will all come back to how you think oxymorphone could fit into your practice, what questions you have about it, and what we can do about that going forward. So this should be a lot of fun. We'll have some nice sections, some interesting data being presented. And thanks to our speakers, as well. So, Dr. Herndon, Dr. Peppin, Dr. Smith, thank you for coming. That's really my main introduction.

I figured before we start, before I have Howard come up and start the process here, I'd like to just introduce myself. My name's Matt Wieman. I'm the Medical Director in the Pain Group at Endo Pharmaceuticals. And I'll turn it over to Todd.

TODD KIRBY: Hi. My name is Todd Kirby. I'm Associate Director of Clinical Science at Endo. Thanks for showing up. Thanks.

MATTHEW WIEMAN, MD: We'll go around the room.

GAVRIL W. PASTERNAK, MD, PhD: Gav Pasternak. I'm up at Sloan-Kettering, and I've been doing drugs for 40 years. [Laughter]

NALINI VADIVELU, MBBS, MD, DNB: I'm Nalini Vadivelu. I'm from Yale University, and I'm an anesthesiologist and a pain physician. So, much of our practice is with acute pain management and palliative care at this point.

HOWARD A. HEIT, MD, FACP, FASAM: My name is Howard Heit, and my main interest is the interface of pain and addiction.

KAREN F. MARLOWE, PharmD: I'm Karen Marlowe. I'm a clinical pharmacist. I'm working right now with the University of South Alabama with the internal medicine group and also with the Auburn School of Pharmacy. And I do acute and chronic pain management and then work with their Sickle Cell Center.

NEIL SHUSTERMAN: And I'm Neil Shusterman from Endo Pharmaceuticals. I head up Pharmacovigilance and Risk Management. I'm a nephrologist by background, but I've been in the pharmaceutical industry for about 23 years now, all in R&D and most of that time in clinical development and drug safety.

JOHN PEPPIN, DO: John Peppin. I'm in Lexington, Kentucky, and now I'm doing palliative care and hospice. Also I have done quite a bit of clinical research in the past and worked in a pain clinic for the last seven years, up until about six months ago.

CHRIS HERNDON, PharmD: My name is Chris Herndon. I work in chronic pain management primarily on the primary care side with family medicine and outpatient internal medicine, and see both civilian and military patients.

HOWARD S. SMITH, MD: I'm Howard Smith. I'm at

Albany Medical College and Academic Director of the Chronic Pain Program, as well as Medical Director of Palliative Medicine there.

STEVEN P. COHEN, MD: I'm Steven Cohen. I work at Johns Hopkins Hospital in the Pain Treatment Center, and I also direct pain research at Walter Reed National Military Medical Center.

MARTIN D. CHEATLE, PhD: I'm Marty Cheatle from the University of Pennsylvania. Long drive. My interest is in chronic pain and pain and addiction, and we're looking for the genetic biomarker of addiction in pain patients.

RONALD J. TALLARIDA, PhD: I'm Ron Tallarida. I'm on the faculty at Temple and also in the Pharmacology Department. And I'm affiliated with our Center on Substance Abuse Research. My most recent activities are involved with drug combinations, looking for synergism to optimize efficacy and minimize side effects.

M. CARY REID, MD, PhD: I'm Cary Reid. I'm a geriatrician and epidemiologist, and I am housed within the Division of Geriatrics at Weill Cornell Medical College. I direct an NIH-funded center that focuses on translational research with an emphasis on pain and aging.

PATRICIA BRUCKENTHAL, PhD, ANP-C: I'm Pat Bruckenthal. I'm the Chair of the Graduate Studies Department in Advanced Practice Nursing at Stony Brook

University in New York. I've been a nurse practitioner in chronic pain management for 19 years, and my clinical research areas is coping skills training for nurse practitioners for patients with pain.

ROB GATLEY: I'm Rob Gatley. I'm the Senior Medical Director at Complete Healthcare Communications. We organized the meeting and plan publications for Endo. My own background is I'm a family physician. I had a practice for about 20 years with a focus on pain management.

MATTHEW WIEMAN, MD: Well, at this time I'd like to say thanks again. Let's have a real interactive session. And I'd like to have the honor or introducing Dr. Smith.

HOWARD S. SMITH, MD: Thank you. So this morning I'm going to go through the agenda real quick to just introduce the day. And then we're going to go through each some slides, the three of us here, but again, the main focus is not to go through the slides. Most of you probably know the material better than some of the folks that came up with the molecule.

So the real issues that we want to get into is the interactive discussion of what's the present and the future, where we can go with some of these, both in terms of maybe clinical research projects, publication projects, or just what your thoughts are in terms of whether certain things are worth developing or not developing or that they may be

useful for clinicians or not useful.

From 8:15 to 8:30, I'm going to just go through some of the meeting objectives. Then I'll turn it over to Dr. Peppin to go through opioid therapy for chronic moderate-to-severe pain management or best practices. Dr. Herndon will discuss oxymorphone pharmacology. Then we'll take a short break. I'll discuss some oxymorphone continuum of care, various different routes and formulations that may be possible in the future.

Then we'll take a short lunch at noon. Dr. Shusterman will discuss after lunch the effect of reformulation of Opana ER on abuse of the product, the early experience from surveillance data. And then Matt and Rob will talk about oxymorphone and pain management, and we'll give some closing statements and be out of here by 3.

So really we want everybody to contribute, everybody to talk, and any clinical experiences, your opinions, really that's what we're after. We're not necessarily after people quoting the literature as much as what your experience has been with the products out there, as well as what you think might be useful going forward.

We're going to get an early start actually. Let me just say that in terms of the best practices for opioid therapy in chronic pain management, touch on risks and challenges associated with the use of opioids, barriers to

successful use of opioids, practitioner knowledge and training gaps, patient knowledge gaps, risk mitigation strategies, REMS programs, best practice development. Oxymorphone molecule for chronic pain, the uniqueness of the molecule as a therapeutic agent, its place or niche in the pain management armamentarium and continuum of pain care, and any knowledge, informational and clinical study gaps regarding the molecule that may spark future publications or future clinical research projects.

Dr. Peppin, as you've heard, is very well-known and well-versed both in terms of literature as well as speaking. His clinical background is vast in terms of chronic pain, as well as palliative medicine. And he's going to discuss "Opioid Therapy for Chronic Moderate-to-Severe Pain Management: Best Practices".

Opioid Therapy for Chronic Moderate-to-Severe Pain Management: Best Practices

JOHN PEPPIN, DO: Good morning, all. Did you all get enough coffee? I have this caffeine deficiency that I have to fill up every morning.

We're going to go over some data. I think most of this is very familiar to you. But opioid prescribing for pain of noncancer origin is increasing, and there's been also along with that increased overdose and mortality,

abuse, misuse, overdose deaths, and diversion. In 2007 there were over 11,000 fatal overdoses. But just to put that in perspective, two points with this. About 17,000 deaths occur per year from NSAIDs taken as directed. And also, and we were talking about this last night, if you look at deaths prior to, say, 1995, something like that -- Howard, we were talking about this last night -- deaths from heroin and cocaine, who cared? Nobody really recorded it.

And so how do we compare that 11,000-plus, whatever it is today, with what happened back in 1990 when OxyContin wasn't around to abuse. Those are interesting questions. And I think maybe at another time we could discuss it, but it's kind of interesting, but something to put it in perspective.

Some states have enacted legislation to limit opioid dosing, improve patient screening and monitoring, and encourage appropriate follow-up of aberrant drug-related behavior. In Kentucky, we just passed House Bill 1, which is a Draconian measure that we could probably talk about in a few minutes.

Also we have Florida and a couple of other states that have put in legislation. Many states that are going to in the future. And I think what this points to as far as my perspective, we're going to see a reduction in the prescribing of opiates around the country because of this

kind of legislation. I think it's going to be problematic in lots of ways.

We don't know, however, whether or not those kinds of legislative approaches have any effect on prescribing or overdose or misuse or diversion. I know they like to point to the fact that opioid prescribing in Florida has gone down since they put that legislation in place, that's true. But we don't look at any of the secondary outcomes. So what happens to those chronic pain patients? I mean, what else is going on there besides just prescribing for opiates? And none of this legislation has any provisions for doing research to look at outcomes, good and bad, or unintended consequences.

So, can implementation of evidence-based best practices mitigate abuse and misuse without creating barriers to care? That's one of the questions that perhaps we can discuss when we're done with these slides.

Physicians are not confident in their knowledge of opioid abuse, misuse, addiction, diversion. In this one survey 70 percent were concerned about actually increasing or facilitating abuse and addiction. And a retrospective analysis of urine drug monitoring programs, 55 percent of physicians continue to prescribe even if there were aberrant results for those urine drug tests.

Most undergraduate medical curricula don't teach

pain management, opioids, addiction, end of life, palliative medicine and giving bad news. And I always ask how many here going through your professional school, pharmacy, nursing, got an hour worth of lecture in pain management? How many folks got an hour? It's amazing. I'll talk to groups of 300, maybe ten hands go up. Much less a course. And of course all of us have pain, all of us die, right? End of life. These are not uncommon things, and it's just amazing the medical schools haven't gotten their act together.

Less than 30 percent of medical schools require opioid instruction. Less than 10 require instruction about abuse and addiction, less than 10 in palliative care and end of life. Mean number of hours, 11. I mean, it's just amazing. I remember when I was in med school, and we had 70 hours' worth of lecture on obstetrics/gynecology. I did a month of obstetrics. I delivered 70 babies. I never want to see another delivery as long as I live. But that's only 50 percent of the population at most at any one time, right? We're talking all of us will have pain, all of us will die at some point in our lives. This was a really interesting statistic actually. Veterinary schools devote five-fold more hours to pain management than medical schools. I thought that was fascinating. That was new data for me at least.

So, what fundamental knowledge do we need to do responsible opioid prescribing? This first bullet,

complexity of chronic pain, is one of the things that I've been doing a lot of thinking about. Dr. Cheatle and I actually are working on a paper along this line. And when you look at the chronic pain patient, these are not simple people that come into my office. These are not people that come in and go, "You know, Doc, my knee hurts. And by the way I have no other diseases, and I have no problems and no psych issues. And I sleep well at night. I exercise." I mean, I don't see people like that. I don't know about you guys, but I never see people like that.

What I see are extremely complex patients, and they've got multiple comorbidities. They've got sleep disturbances and maybe sleep apnea and obesity. And they've got heart disease and kidney failure and liver, and yada, yada. It goes on and on and on. These are not simple patients, and we can't be thinking about these patients in this linear fashion. So the notion that the American Pain Society and American Academy of Pain Medicine I think put out this statement about, "Well, if they come in for back pain, you just focus on their back pain."

I couldn't disagree with that more because you're going to miss the other two-plus pain problems that they have because what we know about chronic pain patients, they have at least three pain problems when they come in to see you. You're also going to miss the fact that they may have

sleep apnea and stick them on methadone, and next thing you know maybe they're dead. And the problem that they may be on benzodiazepines, and there you've got another problem that you need to deal with, et cetera, et cetera. And it goes on. So complexity is a huge issue I think in these patients that we're dealing with.

The clinical pharmacology of opioids, and Howard will go into that and Chris also in much more detail. And selecting the appropriate opioid molecule, I'm not sure how we do that, but okay, we can talk about that. Selecting the appropriate dose and treatment duration, adjuvants and opioid-sparing therapies, which I think are underutilized. At least that's been my experience.

And factors contributing to attractiveness of abuse: molecule-based versus formulation-based attractiveness. I've always felt, and this is an intuitive feeling just in my own gut, that there's something about the oxycodone molecule that's different. It just seems to be a different molecule, and people like it better for some reason. And I'll throw that out for whatever it's worth. But that's oxycodone, not oxymorphone.

Also, benefits and limitations of abuse-deterrent formulations. Steve Passik always says that you give me a product that you say is abuse-resistant, and I'll give it to a guy named Vinnie in the Bronx with a spoon and a lighter,

and he'll have the drug out in about 30 minutes. So I mean, these people are very good chemists. It's just amazing what they come up with. Appropriate and inappropriate use of abuse-deterrent formulations, those all contributing to the attractiveness of abuse.

And detection and management of aberrant drug behavior. I really feel that patients need a complete evaluation when they show up in your office for the reasons of, number one bullet up above, but you just need to know what's going on with them. So I mean, I've had patients where the family history gives me the diagnosis. "Doc, I've got numbness and tingling in my legs and my hands. I don't know what's going on. Oh, by the way, my mother had Charcot-Marie-Tooth." Okay. You know, those things can be helpful at times. I think it's really important. And this has to include psychological evaluations looking at comorbidities, other medications. Most of my patients are on at least 10, 12, 14 meds. And so we need to understand not just are they abusing the opiate, but are they on Xanax that they're buying off the street. And patient opioid treatment agreements can be helpful, as well.

So we have this thing called REMS, and this is for long-acting and extended-release opioids. The final version just came out. I mean, the REMS that came out is just a RISKMAP really. It's no different than the RISKMAPs. Never

been shown to reduce abuse, misuse, diversion, overdose, deaths. I mean, let's be honest, okay? You go to the pharmacist and they give you that little printout that talks about the drug you're going to take, your antibiotic. How many people have read it? Okay. I'm not putting up my hand because I've read it, by the way, because I don't read them either. [Laughter]

So they're going to hand you something that says, "Oh, by the way, don't crush it and inject it." You think that's really going to make a difference? I mean, it's just ridiculous to think that that's going to make a difference. Anyway, if you want a critique, we've published one in *Issues in Law and Medicine*. But I think the REMS really is a waste of taxpayers' money and a waste of effort. But it's there, and we have to do it, so such is life.

Focus on education to ensure the prescribers understand opioid pharmacology. Very important. I had a pulmonologist when I was in Des Moines practicing, who said, "Oh, a narcotic's just a narcotic." I mean, how silly is that? It's like saying, "Oh, you know, a blood pressure medicine is like a blood pressure medicine. It doesn't matter whether it's a beta blocker, calcium. They're all the same." I mean, that's just silly, right? And opiates aren't all the same. They're different, and they have different issues.

Risks and benefits of opioid therapy. Important to understand that hydrocodone is a risk, and just because it's a Schedule 3 doesn't mean you can write for ten a day and people aren't going to get themselves in trouble. Proper patient selection and monitoring, I mean that's a huge issue.

And how to recognize opioid misuse, abuse, and addiction, which a lot of times I still hear this amazingly in the hospital: "Well, they're addicted." "But what do you mean?" "Well, they're on a narcotic, a fentanyl patch every three days, so they're addicted." Well, they're not. This is just a misunderstanding of what these terms are. And I also think we have a problem when it comes to REMS, that REMS has not defined what these terms mean. So what does abuse mean? What does misuse mean? What is an overdose death, by the way?

So you think intuitively, we go, "Oh, overdose. We know what that means, right? You take too much OxyContin, you die." But most of those people, as has been shown in the literature, it's polypharmacy. So they drank a bottle of vodka, they shot up some heroin, they took an OxyContin, they took a couple of Xanax, and they died. Well, what caused their death? It's not so simple. It starts becoming very complicated.

So the REMS is voluntary. Physicians at this point

are not required. There's of course no REMS for hydrocodone, the most abused opioid medication in the United States, or oxycodone combination products. A survey of 259 physicians found that 48 percent would comply with the REMS, 10 to 18 percent stated that they would discontinue prescribing if the REMS went into place.

I will tell you that just empirically in Kentucky, I know a number of primary care doctors who have told their patients they will no longer prescribe any scheduled drug, period. So you don't get Lyrica, you don't get any benzos, you don't get anything from them. The benzos are okay, by the way. I had benzos. I'm a benzophobe. But we're seeing a lot of primary care docs just saying, "We're not going to prescribe them for kids. If they have ADHD, we're not going to prescribe. You're just going to have to go somewhere else." It's becomes a real serious problem in Kentucky I think.

PDMPs, prescription drug monitoring programs, these gather data. Correct me if I'm wrong if any of you know different, but I don't know of any PDMP in the country that does research on the data that it has, and many of them you can't even get into the database to do research. So up until fairly recently, KASPER, which is probably one of the premier PDMPs in the country, I couldn't get in. If I said, "I want to do a study on X," I would not be allowed to get

into that database, even if the data was clean and was unidentifiable. They've changed that recently, but you have to actually submit a proposal to the cabinet and all this crazy stuff, so it takes quite a bit of time. But that's just nuts, right? I mean, this is a huge database that we could gather some great data from, and they don't allow us] to do that.

Acquisition of controlled substances by doctor-shoppers and KASPER does identify those initiatives undertaken by regulatory health and law enforcement agencies, again gathering data for them. But PDMPs have never been shown to achieve the goals of reducing abuse, misuse, diversion, or overdose deaths to my knowledge. And KASPER is probably one of the best. And since its inception, opioid prescribing has gone up dramatically in the State of Kentucky, as has overdose deaths.

So, here are some questions. How are the social concerns of abuse, misuse, balanced with the needs of patients who are in legitimate pain and would benefit from chronic opioid therapy? A huge and important question, and I think something that a lot of docs don't think about, primary care and others. When they just write a script, they don't think, "Could this end up in the hand of a kid in high school? Could this be abused? Could this be sold on the street?" I mean, I don't think that's something that just

comes to their foremost mind, although I think we need to be responsible and consider the social consequences.

And what are the best practices to achieve this balance? So educational initiatives, I mean, I'm very skeptical frankly of CME programs. If you look at the literature on CME, it's not robust. I mean, CME doesn't change physician behavior and prescribing patterns generally. So we need to come up with more unique and creative ways of approaching doctors and changing their behavior. 2X4s, I don't know what. And changing our behavior, right?

So publications or other media. I mean, publications may make more of an impact. Mentoring certainly makes a big impact. REMS I think is a waste of time, but that's my opinion. And medical education. How many docs here think you could go back and take one of the tests in medical school and pass it today? I don't care, any test, right? I mean, I think I'd flunk. Histology? So I wonder what that education actually gave me, but that's another question. And postgraduate education.

And of course that's where we get a lot of our prescribing patterns. Why do I use Darvocet? Well, my attending used Darvocet when I was a resident, and his attending used Darvocet. And it just goes back and back and back without really thinking. So, Howard, are you going to

lead?

HOWARD S. SMITH, MD: No, go ahead. Why don't you start off interactive discussion.

JOHN PEPPIN, DO: Any questions, comments from you? Yeah.

GAVRIL W. PASTERNAK, MD, PHD: One point you don't have up there is culture, because years ago at Cornell, before they revised their curriculum, we had fairly extensive education on opiates. They received three to four hours of lectures on opiates alone. We know that they actually heard what we said. They passed the test. The same people went on to become interns and residents, and they went back to the old prescribing habits because that's what everybody did. So it was clear that they heard us, but they never believed us. And I think that one of the issues that you really have to address here is whole culture of pain. We live in a John Wayne society where you're supposed to be tough, and people don't necessarily believe things even when they're told by the, quote/unquote, experts.

JOHN PEPPIN, DO: So how would we change that? I've thought about this a lot. I'm not sure I have any answers. But how would we change this culture?

NALINI VADIVELU, MBBS, MD, DNB: Actually for the last five years, we have started a program. It was initiated by the students themselves, because it got to a point that

we've had so many interns coming on to service on day one, don't know how to write a PCA and stuff. People are getting like respiratory depression or they're getting under-prescribed, and so many complaints from patients, attendings, and everything. So the medical students approached us, and they wanted some program themselves.

So we had the student-led initiative for the last five years. Actually they asked me, and I was like a junior. So I worked with them. But then now it's expanded to the extent that now we have a multidisciplinary faculty involved and we have it formally in the curriculum for the last five years, first as a student-led thing, initiated, but now we have all the faculty involved, and now we have all these courses. It's formally in our real medical curriculum.

So I really agree with you that we have to start with this education of these doctors because many of them going on to rural practices everywhere, and they are having problems. And it's not just of a few pain trained doctors to take care of this thing, but every physician and nurse has to be able to take care of pain to some extent. So education is really good.

JOHN PEPPIN, DO: Is it changing the culture there?

NALINI VADIVELU, MBBS, MD, DNB: Yes. It started. But it came to the point that the students themselves had a big thing, and they raised the funds, and that's how we've

been running this program for the last five years. But now it's become that Yale, the dean and everyone, medical Sloan-school dean, they opened their eyes. And now they are putting together this big multidisciplinary group, including surgeons and psychiatrists, neurologists.

JOHN PEPPIN, DO: Surgeons?

NALINI VADIVELU, MBBS, MD, DNB: Yeah, yeah, yeah. Actually he's the chair of the pain committee, Dr. Leslie[sp?] right now.

JOHN PEPPIN, DO: Wow!

NALINI VADIVELU, MBBS, MD, DNB: Yeah, I was the one documenting [?]. But the student initiative is still my thing. I still am chair of that. But it's good. But even physicians, like practicing doctors, need to get educated, not just undergraduates where we can start with.

JOHN PEPPIN, DO: Howard.

HOWARD A. HEIT, MD, FACP, FASAM: What we're doing is the discussion has started out as how we educate the people who are in training. And that will help possibly, and I emphasize possibly, next generation of doctors going out there. The question that also should be a focus of this meeting is how do we facilitate change of physicians already in practice. And that's very hard to do because again, two things. What's in it for me? When it's not about the money, it's always about the money. We have insurance issues, the

dysfunction of our health care system as far as reimbursement. And how can we educate the physicians or the prescribers in practice as we sit here now? And I think the company should bat around ideas of how we could do that in regards to facilitating change. How do you facilitate change in people who are already in practice?

JOHN PEPPIN, DO: You think it can be done, right? Because I think it can be done with creative approaches, but not with just kind of the standard talking heads.

HOWARD A. HEIT, MD, FACP, FASAM: I think a lot of physicians don't prescribe or prescribe poorly because they haven't been educated. I remember the first time that we had a spinal tap, we heard "Ffft!" We thought the brains were in the syringe. [Laughter] A little bit, a little part of it. And I always thought the possibility that at a pharmaceutical company, the reps have maybe two, three minutes with a physician at most, and what if they became fact people. They came in with laminated cards and taught one or two facts. They weren't sort of like repping the product; they were repping education. And by a byproduct, they would say, "Well, the [person from] Endo is educating us. Really not talking much about their product, but he gave me a laminated card that I could put in a folder that says what addiction is, physical dependence, what is tolerance, which boundaries should I set, how do I interpret urine drug

testing."

And every time the rep came in, he became the fact person, and it's sort of like a joke in that area. And the physician then accumulated laminated cards in regards to education. We've got to think about the people who are already in practice.

JOHN PEPPIN, DO: I agree.

M. CARY REID, MD, PhD: I would echo that there are tools. So, better methods of surveillance and evaluation and helping physicians understand that the treatment really does make a difference, particularly in the area of function. What I also feel is missing from the person is the other part of this, which is changing the culture at the patient end. I'm a geriatrician. It is often very difficult to get an older person to take the medication. There is fear of harm, fear of addiction.

And so you can do all you want on the prescribing end, but if you don't get patients who are willing to take the medication or take it in a way that either they're nonadherent or they abandon therapy after a week, you've got problems. So there have got to be more innovative methods of helping to change the culture of the patient population.

GAVRIL W. PASTERNAK, MD, PHD: A lot of times we face a real issue, and getting back to the culture. Pain doesn't kill you. The drug to treat pain could kill you. So

that's a very basic issue. Not prescribing opiates doesn't put you in jail. So these are all parts of our culture in the US. Obviously the patients are an issue, as well. But you can do all the education that you want to do.

And I have never been more impressed with observations than when Kathy Foley started with discussing pain for their medical students, and all of a sudden they started coming in to their house officer training, and all of a sudden it wasn't just one medical school where everyone had the same training.

All of a sudden now, the Cornell graduates at New York Hospital were only a small fraction of the people that were in there, they were coming in from all the other sides, and their attendings, who had experience in this, they just didn't believe it. So the real question is education is great, but if you don't believe the person when they tell you something, you can tell them as many times as you want to. It's not going to do any good.

JOHN PEPPIN, DO: A quick procedural question? Are you getting all this recorded?

FEMALE SPEAKER: Right.

JOHN PEPPIN, DO: You're hearing everybody? Do they have to hit the mic switch? Okay. Marty.

MARTIN D. CHEATLE, PhD: Not to be a pessimist, but most of medical practice is driven by dogma and myth, you

know, and that's what you were saying. You can educate all you want. We at Penn, we're probably one of the only medical schools that every medical student has to take 25 hours of addiction medicine. Now, how much does that translate, I'm not sure.

And I think the only way to deal with this is that we have to have policy changes. You can pay [?] all you want, we need to incentivize people. And where it has to start is primary care. 55 percent of all opiates are written by primary care. They're beleaguered. They don't have the time. They don't have the resources. And you have to incentivize them from an insurance perspective, "If you do the right thing it will be more dollars in your pocket."

And that sounds very pessimistic, but it's very realistic about it. If you look at the changes that have been occurring in substance abuse treatment, now we have a parity act that was pushed through, which is substance abuse is treated like other medical conditions. I can guarantee you that's going to shift the treatment of substance abuse treatment. So I think what Endo can do or other pharmaceuticals is to actually work with insurance companies about changing the way they pay for these services. So you ask a doc, "Here's this wonderful algorithm." I went to this family doctor and said, "I have a great algorithm for you." And he opened the drawer and he throw out ten more, and he

goes, "I have an algorithm for everything, and I don't have time to even follow these." If we pay for them to do a complex evaluation and treatment and risk mitigation, that will change the behavior. But I don't think education alone will.

JOHN PEPPIN, DO: That's what you were saying. Other comments?

STEVEN P. COHEN, MD: I work in two clinics, so one in kind of an inner city at Johns Hopkins, a pain treatment center, and one with military personnel at Walter Reed. And people come into our clinic and we can do procedures on them. We can prescribe adjuvants to them, refer them somewhere else. We can prescribe opioids. And this is basically a very strong consensus: Opioids help a lot of people and they harm some people.

But about 90 percent of the time that we spend on the phone arguing, answering complaints, are from opioid patients, the small percentage of patients who do really poorly. And this is a big problem. I don't know that opioids carry a higher risk than putting in a spinal cord stimulator or doing like discography. But those things are simple things to do. You get paid for them, and then that's usually it. But with opioids, even if you prescribe correctly to nine out of ten patients, that 10 percent of patients is going to make your life really, really difficult. And it's

going to impact on your time, it's going to impact on your bottom line. And this is a big problem.

JOHN PEPPIN, DO: Do you think it matters what you're giving that 10 percent? I think they're going to be a problem regardless of what you give them. There may be other issues if you're giving them opiates, but they're still going to be calling you up and it's still going to be a problem. And nothing works.

STEVEN P. COHEN, MD: No, no, no. But the problem is so you prescribe opioids to people. I know there are a lot of ways. There are all these risk stratification tools. You can try to identify the people who will run into problems with opioids. But nothing is 100 percent sensitive. You're going to miss people both ways. You're going to miss people who might benefit that you don't prescribe, and then you're going to give medications to people who are going to end up running into problems.

And like I said, just even from like a selfish perspective, and it's the same thing with primary care docs, it's much easier to not give medications to people who you're not sure about, even if most of them will end up doing well.

And like I say, this is complaint after complaint from our front staff, from our residents, from our fellows. It's complaint from commanders with people missing days and

losing opioids and having problems. And now in the military that's grounds for immediate, you know, boarding people out of the military. And you can selectively do this. And we have people all the time who escalate doses, and some of them are doing well. But the cancer patients and the old patients we don't ever say, "Oh, they have opioid hyperalgesia."

We kind of selectively say, "Oh, this person he's calling our clinic all the time. He's coming in. He has opioid hyperalgesia." And we use this. It's kind of the same thing. I think people see things selectively in the way that's going to be in their own self-interest. It's not always conscious. It may be subconscious. And this is a big thing that's going to be very difficult to overcome.

JOHN PEPPIN, DO: How do you think Endo could address that problem. I mean, do you think that they could address that with education?

MARTIN D. CHEATLE, PhD: Well, but I think what the literature shows you is that people who stay on opiates chronically -- most people don't. They take it for a while and they stop. Some of the work out in Kaiser, they looked at all the ICD-9 codes. People who stayed on opiates greater than 90 days had more psychiatric comorbidities, more ICD-9 codes around substance abuse. That's what you're saying is that these people that are on chronically, they have all

these comorbidities that you're really trying to treat as a pain anesthesiologist or a primary care doc when you really don't have the tools to do that in most places.

Maybe at Hopkins you do, but most people out in the community, someone comes in with psychiatric problems and substance abuse problems, they have limited resources. So I think that again it's a policy issue of making sure that patients have the ability to try all of the comorbidities. And it means that the opioid molecule can be very effective if we co-treat all of these other problems and sort of mitigate that risk. But those are the people that give us problems.

HOWARD A. HEIT, MD, FACP, FASAM: The concomitant [?] care, a number of us tried X number of years ago, failed miserably financially. I think also unlike other disciplines, there's the white elephant in the room, and there's the legal, there's the DEA, et cetera. And it's not called insulin-addicted diabetes. It's called insulin-dependent diabetes. I think physicians, there's a lot of fear out there. And if I don't prescribe it, then I don't have to worry about it. If I do prescribe it then I do have to worry about it. But I think we also have to teach the physicians who are in practice what I call the rules of the game, which are changing tremendously on the state level every day, let alone what's changing on the federal level.

GAVRIL W. PASTERNAK, MD, PHD: The other question is education is wonderful, but who has the right answers to teach? If you go to ten different medical centers, they'll have ten different ways of addressing the same patient. Which one do you teach? If you teach the one at the place that is used as the place you go to, they'll say, "Great." If you go to the next one, they'll say, "I don't believe it."

So part of the problem with education is the fact that there really is no correct answer as to this is how you should do it. Many people have devised many different approaches, and many times they all work reasonably well. So how do you decide which one to teach? And this gets back to what I was saying before. You go in to teach people, and they don't necessarily agree. They hear you, but they don't necessarily agree with you.

NALINI VADIVELU, MBBS, MD, DNB: Only 3 [?] percent of the oncologist medical schools in all of USA has formal medical education anyway. So that has to be developed. There's a lot of room for education to even start to know what is working or not. Because most schools, maybe whatever percent don't even teach anything formally.

JOHN PEPPIN, DO: You were saying, Gav, that when you teach the medical students, they hear you.

GAVRIL W. PASTERNAK, MD, PhD: Oh, yeah. They can

answer the questions. But they don't do it.

NALINI VADIVELU, MBBS, MD, DNB: But then when they go to some other institution, it's different.

JOHN PEPPIN, DO: It may not be that they don't believe you. It may just be that when they get into the culture of doing the clinical rounds, et cetera, that, "Look, my attending wouldn't go along with this, and I don't want to be an outlier because I want to pass."

GAVRIL W. PASTERNAK, MD, PhD: Who do you believe? And when they get into those situations, they have a very close tendency to believe the mentor that they're following around in the ward, because after all, that's the person they're closely allied with, and that's the person who presumably has all the experience.

MALE SPEAKER: I think there's something important that Howard brought up. Nalini was talking about undergrad, and Howard was talking about when doctors are in practice. The two are really linked because the attitude at Yale that you're describing, Nalini, with student-led activities and students bringing forth what they don't know.

NALINI VADIVELU, MBBS, MD, DNB: Because nobody wanted to pay any attention or invest in anything for education. They were like, "Whatever. We just need to get the work done, get practice done. That's what's happening." But then they are the ones who started it. They said, "We

don't even know. Somebody dies on the floor, and then you are looking at us like we didn't know how to prescribe it." You see? So that's what happened. Something adverse happens and then things start.

JOHN PEPPIN, DO: So we have two different situations here. So what I hear you saying is that the culture has actually changed.

NALINI VADIVELU, MBBS, MD, DNB: It's changing, yeah, at Yale at least. But it's one of those (inaudible) schools.

GAVRIL W. PASTERNAK, MD, PhD: Here's a classic example. Our general surgeons now post-op, and this is Sloan-Kettering, where we'd like to think that we know how to treat pain. We've got a long history of education and a long history of everything else. The general surgeons after big surgeries, you know, Whipple procedures, the patient is put on a PCA. There's no basal. And the surgeons go, they can just click the button, and the rationale was they had a patient a couple years ago that was on a basal. It was probably too high. The patient died. So they refused to put anybody on a basal. There's only one trouble. The patient decides to fall asleep, and they don't press the button, they can wake up in an hour with the equivalent of zero pain meds.

Right? And this is after a major surgery. I don't

consider this to be reasonable pain management, but it's based upon one experience, one anecdotal issue, and it changes everything for everybody. And now all the surgeons that come through, this is the way that they're taught to write their orders. And they think this is the right way of doing it. So when someone comes in and says, "No," who are they going to believe?

ROB GATLEY, MD: So just given you guys' experience, I'd like to know how do you change our culture? How do you encourage students to question their mentors? "Why are you prescribing Darvocet? Why is there no basal?" I don't think that culture really exists in most med schools. You usually should defer to your mentor. You don't question. That kind of thing is not encouraged. So that's a key change that needs to be made that sort of links the doctor in practice to the student issue.

GAVRIL W. PASTERNAK, MD, PhD: That's going to be very hard for a lot of reasons. First of all, you want the recommendation. Secondly, if you didn't think the doctor you're following was great, you wouldn't follow him. It's hard. And as I said before, the bottom answer is there is no right and wrong. Many people do it many different ways, and they figure out ways to get it to go. How do you convince somebody that this is the way?

JOHN PEPPIN, DO: Thoughts from anybody else about

that?

PATRICIA BRUCKENTHAL, PhD, ANP-C: I just want to add a little bit. I think the setting for which we're teaching the skills also matters. So for example, I work in the chronic pain arena, and somebody was mentioning the sort of 10 percent are the more challenging patients. And so how do we teach the practitioners the skills that they need to deal with that patient population? And then when we do that, is there even access to the types of resources we believe that those patients should have.

And so we all know that at least in my region it's difficult to find addictionologists to help co-manage these patients with. Or do we as practitioners have the skills to teach self-management skills to patients and help motivate them to more positive behavior change? I think that the equation is just very difficult, and the game is changing. So we have to look at why we need to move towards teaching patients more self-management and maximizing their own self-care.

HOWARD A. HEIT, MD, FACP, FASAM: I'm in private practice. I think what determines who you take care of and who you don't take care of is your comfort level, your education, and your resources that you have in your particular area, and then the overall arch of it is again what time do you have, what's the insurance reimbursement,

et cetera, things of that nature. So we're looking at a multifaceted problem that needs multifaceted solutions to it. And we have to sort of like pick one or two areas and hone in on it and say, "Where could we possibly make changes or possibly make suggestions?" as opposed to holistically look at it. Because we could be here for days and days and days and days looking at every aspect of it.

JOHN PEPPIN, DO: Marty.

MARTIN D. CHEATLE, PhD: I also think there's an opportunity for electronic medical records to do some of this because it's a time issue. If you try to tell someone "You have to learn how to do addictionology and you have to learn how to do risk stratification, all within five minutes in your office visit." And we've been working on some modules that you actually embed in EMR. So like a lot of the systems, like Penn uses Epic, and it's like a stop order, so you can't get the patient out of the room unless you do this next step. And that would change some of the behavior, and that's an opportunity for pharmaceutical companies to sort of partner with these type of opportunities. And we put stop measures in where the resident or fellow again has to do these steps before they can sign the patient out. And then it starts changing. You're embedding the education and the treatment practice within the electronic medical record. That might be one opportunity to sort of change some of

this.

ROB GATLEY, MD: That's a great point, Martin, because that's the kind of thing that Endo could be involved in. Some of these things are institutional with universities. But there's a lot of initiatives beyond publications that Endo could be involved in. A lot of pharmaceutical companies are moving into electronic medical records.

MALE SPEAKER: And with the Affordable Care Act, everyone should be based on an electronic medical record in theory, so it should affect people in private practice also that are part of health systems. Great opportunity, honestly.

HOWARD S. SMITH, MD: It will be valuable for us to brainstorm that kind of thing now.

MALE SPEAKER: Unfortunately they don't all talk to each other from what I understand.

MARTIN D. CHEATLE, PhD: Well, it's funny. When you put stop orders in and they want to get that patient out of the room, all of a sudden they start following procedure because they have to follow through one step after the next.

JOHN PEPPIN, DO: Dr. Reid.

M. CARY REID, MD, PhD: So to me an underlying assumption here is that opioids are the right course of action. And I would argue that for many chronic pain

conditions we simply don't know that to be the case. There is a huge gap in the knowledge base around the long-term benefits and risks of opioids, particularly in older adults. I think generating that evidence would go a long way to helping clinicians feel better about prescribing. You mentioned the electronic health records, I'm familiar with the patient registry that Chuck Enterisi[sp?] and others are building at Sloan-Kettering and Cornell Hospital for Special Surgery with 2,000 patients connected where they routinely collect a variety of data, including diversion data prior to each visit, and all of that is integrated in an electronic health record.

And they will begin to generate their own evidence base to help them understand which patients are doing better, which ones are not. And it seems to me that supporting those kinds of activities would go a long way to help providing evidence to clinicians that they're doing the right thing.

MARTIN D. CHEATLE, PhD: You know, it's interesting, Jane Ballantyne out in Washington, she's trying to get this project through where actually before the patient can get their first prescription of opiates, they have to do an online education and pass a test. So before you get that first script, they have go to through and take a test, have a knowledge base before they do it.

MALE SPEAKER: It's interesting, if people own computers.

GAVRIL W. PASTERNAK, MD, PHD: The other part about this that I think we may not be thinking about as much is that teaching how to use opiates is very much in my mind an art. We have a tendency in modern medicine to do clinical trials and to do 2,000 patients. But the basic underlying assumption that we have a homogeneous population. When we do animal studies in the laboratory, we get unambiguous results.

Why? Because all our animals follow the rule of the Ozarks, which is that everybody is intermarried with everybody else. So we've got this very homogeneous genetic background. And in people that's just not the case, both genetically as well as culturally. And so what may be good for 60 percent may not be good for the other 40 percent. Drugs that may not pass muster against placebo may still work very nicely in 30 percent of your population. And we all have examples of those things.

So it's not like one-size-fits-all medicine, and I think that's the most difficult thing in terms of the physician. Yes, patient A has chronic arthritis and would do well on opiates, but patient B, with very much of the same symptoms, has a tendency towards abuse. How do you tell them apart? So part of me gets very antsy when we start talking

about statistics and large populations because in fact it's really every patient is an experiment with an n of one. And how do you get that out there? It's like teaching them how to be a painter. You can teach everyone how to be a painter, but not everyone's going to end up Michelangelo. And there's just an awful lot there that's more than just following a card with the rules.

JOHN PEPPIN, DO: That's absolutely true. There's been a literature on clinical research, and so you have a placebo-controlled, double-blinded trial. You've got 500 patients. But this is a rarified population. I mean, you don't have the 94-year-old. You don't have the renal failure. You don't have the liver failure. And so what do you do with this population? And I look at these studies, and I think, "I don't have too many patients that fit this narrow enrollment criteria. Mine are way out here somewhere." And so does it really apply? It's a really good question. And I'm not sure Endo can answer that question.

NALINI VADIVELU, MBBS, MD, DNB: Can I just say one thing, please? And that is like I see everyone in the room is probably born here and brought up here and lived all their lives here. I have been here for 23 years, but before that I was born in India. But what I want to say is there's a big whole world outside USA, and even Endo, I would urge that you would start looking at markets other places. Like

85 percent of the world's opioids are being utilized in the USA which has only 5 percent of the world's population. So we are looking at something Steve Cohen just said, that you have all these extra problems because of these opioids. So I think if we have a global distribution better, even your market will get better for Endo, it will be much better. And people who really need it in other places internationally, we can help too. So it's going to be helpful for everyone, and probably we might have less of these other extra -- those 10 percent opioid problems that you see.

JOHN PEPPIN, DO: That's a really good point. One of the things that I have thought, maybe some people have some thoughts along this line, but I've always wondered if we were to compare how we treat patients here in the United States with how we treat patients say in the UK or Europe, because again, we use so much more opiate here. Now, if the outcomes are the same, and of course you'd have to define exactly what that means, but if the outcomes end up being the same, then it really brings into question what we're doing and what are they doing that gives them the same outcomes without using all those opiates. I mean, I think that's a really good question.

NALINI VADIVELU, MBBS, MD, DNB: They probably need it and nobody is even going there to even give it to them or sell it to them. And they'd buy it. It's not like they are

really starved of money. I mean many countries are not literally that poor outside the USA.

JOHN PEPPIN, DO: Karen.

KAREN F. MARLOWE, PharmD: And even within the US, many of the patients I see come from rural areas, and they don't have access to health care. They drive two and three hours to get a diagnosis. They're not going to come back. They're going to get a care plan, and then they're going to go back to a primary health care provider who's a rural health care provider who may or may not be willing to carry out that health care plan. And so are they going to have access?

And I think that's something that we've got to provide the tools that are either the education tools or the care plan tools that somebody's going to be comfortable with going on with that care plan. So can we prop them up, can we give them prescribing tools, education tools, patient education tools?

Most of those patients' literacy level is well below those that live in cities. I know in the Southeast and certain areas of the Midwest, these patients have a lower literacy level. Their health literacy level is lower, their reading literacy level is lower. If we look at most of the things that are being provided for patients, these medication guides, most of them are on a sixth to eighth

grade level. Patients aren't reading on a sixth to eighth grade level in many of these areas. We've got to reduce the level of some of these things we're putting out. We ask why our patients aren't adhering? They don't understand what we're producing.

And we've got to provide them with something that's more appropriate for them and for their education level. I think that's another thing that some of us can help with, is to try to target not only the education materials for us and for these rural health care providers, but also for the patients.

JOHN PEPPIN, DO: That's a theme that I've heard from a number of people about educating patients. I've seen companies before come out with printed materials and stuff. I frankly don't think that has any effect at all.

KAREN F. MARLOWE, PharmD: Make sure it's printed at --

JOHN PEPPIN, DO: Okay, then how would we do it? But let's don't take the rural Kentuckian who can't read and has no teeth. Let's think about maybe a little broader notions. But how would we approach a patient say in Lexington, Kentucky, who's maybe got a bachelor's and they working and they've got chronic pain. But you know what? They don't really understand how to deal with their medicines. How would you do that? I mean, they're not going

to read printed materials probably. Probably not.

KAREN F. MARLOWE, PharmD: No.

JOHN PEPPIN, DO: So what would you do?

KAREN F. MARLOWE, PharmD: I think the patients I deal with now, despite some of the challenge they have, they are engaged. I've been very surprised. I've had an adherence project going on. I have not been able to get them to read materials, but they are engaged on their phones. They will listen to things on their phones.

And so we've been able to use some audio things. We've been able to get them to listen to things. While they've been waiting in the back, we've been able to get them to listen to some phone apps and things. We've been able to get them to listen to some audio files. They do sit in our offices waiting on us. They won't sit there and read, but they will sit there and listen. I think like you said earlier, getting out of the box, giving them a four-page spread with 1,000 adverse reactions, they won't look at.

But if we give them something that's more focused. The Indian Health Service uses a form of patient teaching that emphasizes three points. Patients are likely to learn three points at a time and remember three points. Can we pick out three points that we're going to teach them each time? And so can we teach them three points, and then each time they come in try to teach them three points. You know,

this is your dose. This is how to take it. This is what. So have some form of education that says, okay, on the first visit, this is the three points, the second visit. What is it? Some form of education where each time teach, reteach, assess, and try to get them through.

JOHN PEPPIN, DO: What about TV? The previous clinic I worked at had a company came in and put up these TVs, and they would do educational stuff: talk about nutrition, exercise, stuff like that. So you've got your patient sitting in the lobby, and that's all they've got. It's not *Jerry Springer*, you know, it's how to eat and how to exercise. And I'm not sure. I don't know if it had an impact or not. But do you think something like that would have more of an impact in offices, rural offices? And maybe Endo could help develop that and work with a company like that to get those on the wall?

MARTIN D. CHEATLE, PhD: But I think that's a great point. Even in Philadelphia, half a million people are illiterate in Philadelphia. Me being one. [Laughter] But I think smart phone apps, like you were saying, and a colleague of mine has been doing work with addiction, and addicts who are really hard to manage. And everyone says, "Well, but you're not getting to the poor." Over 80 percent of people who live below the poverty line have a smart phone. And they've been doing smart app applications to keep

people from relapsing. And they have this feedback loop with the smart phone, which you don't have to be literate to use the smart phone. And so maybe I think taking your point and just sort of looking at smart phone apps that you can do, driven by Endo or other companies to do that, so you have this feedback loop. And it cut down calls to docs' offices because they had all this information all the time in a form that they could really learn from. I think that's a great idea.

ROB GATLEY, MD: Just something I'd like to interject here. There's so many hundreds of thousands of smart phone apps and resources online, blogs online. I think reliability of information is a huge issue. So how much do you think it would matter that your patient has been recommended to an app or to a website by you instead of just hitting the Google search and looking at whatever comes up?

KAREN F. MARLOWE, PharmD: I think you have to discuss reliability of information with them. They come to you with information they've found, at least the patients I see come with information they found. And so I think every day we're forced to discuss information. And I've found my pain patients are some of the ones that come more often with information off the web. And so I think being able to discuss or being able to send them to something with an app that would perhaps schedule their medications or put them on

an adherence monitor. I've used that with patients with adherence issues before, ones that I've liked. I think if it came from me and it was something that I preferred, I think they'd be more likely to use it. And I would rather send them to something than have them come with something that I didn't trust.

JOHN PEPPIN, DO: Explain an adherence monitor, what is it?

KAREN F. MARLOWE, PharmD: So, you think about the pill box, like the old-fashioned pill boxes. Patients still use those, but this is more of a pill box on your phone. It alarms. It's specifically set, "Okay, take your blood pressure medicine now. Take your whatever now." And so it's a daily reminder set at certain times so that you take your medications at a certain time.

Or to me, if one could be set up for pain management so that it was almost like a pain diary. There are ones for diabetics where it tells them to take their insulin, and they also register their glucometer readings and different things. If one could be set up for pain management to where they could enter their pain scale, say they took their immediate-release or if they took breakthrough meds at the time when they took their pain scale, and it also reminded them to take their chronic pain meds. I mean, that's the kind of app that I think would be

very helpful if they could then download it before they came in.

M. CARY REID, MD, PHD: We know you have an adherence with these kinds of apps. I worry a little bit about asking too much of patients who are complex. We heard, are they going to do everything that's required? But I love the concept because we've talked about the application from an education standpoint, from an adherence standpoint. I would go back to evaluation and feedback loops. And if you could create a system where imagine prior to going on the opioid your function level is X, and after opioid it's increased fourfold, that kind of positive reinforcement I think would make a difference and moderate treatment effects. And all of that can be done by these apps. But worry about building too much into any one app.

MARTIN D. CHEATLE, PhD: And I would suggest you look at this addiction literature. I can find the references. Because these are really difficult patients, the addicts, and they have nothing but these feedback loops. Their primary therapist is always getting data back all the time. So when you see them in the office, you have this wealth of data. And the patients like it because they grew up on video games, and they love pushing the buttons, and it becomes kind of interactive for them. So they'll put in some data, and then they'll get feedback from somebody before

they even come back into the office. And that improved adherence. It reduced relapse. And so they've done it with addicts.

PATRICIA BRUCKENTHAL, PhD, ANP-C: This is also a great tool for clinicians. We just ran a pilot using the patient-reported outcome data from the PROMISE project. And so patients can then go in in the waiting room and access the database and look at their pain and function and other levels, whatever types of outcomes you're looking at. And then interventions take place, and then they rerecord that. And so you do get a trend line as the clinician over time that you can share with your patient and say, "Well, we've done this," and it's either improved or not improved care. I don't have it, but the outcomes of our pilot shows that the clinicians liked using that, the patients liked looking at that.

JOHN PEPPIN, DO: So it's a really good idea, and we have a possible study, too, right? We could put this in a pain population, look at it. I mean, that would be really interesting.

STEVEN P. COHEN, MD: So I think education is great. That's really going to be a key part of this process in the foreseeable future. But I think at some point also that the people in Endo are going to have to make a strategic decision as to the content of the education. And I

think that there are two paths that you can go by. So I think opioids are helpful to people. I think that maybe they help more people than they harm in the long term. But there are some people that they don't help. And we know those people. Maybe the person with fibromyalgia who is a chemical coper, or someone with poorly controlled psychiatric problems and poor coping skills.

And so if you look at some examples, I mean in the 1950s people knew that cigarette smoking was not good. But the companies, what they did is they buried this data. And these companies are vilified. They're not held in very high regard. And it's not just because they had a product that was not good because lots of companies have products that are not good, but it's basically because they tried to bury that information. So they put profit ahead of really the welfare of the country.

Take a look at the NFL, what they're trying to do. This is a really smart guy who runs the NFL, Roger Goodell. And they've had a problem with this traumatic encephalopathy for with while. I mean, they've made some mistakes along the way. But instead of trying to bury this data, they're really putting a lot of money into research. They're saying, "Yes, we have a problem. Some people are harmed, and this is what we're doing. We're considering changing the rules. We're finding people who break these rules." They put aside

billions of dollars in pensions for people who were injured in the past that they didn't have to do.

And so at some point, you're to have a choice to make. And people are not stupid. Doctors are not stupid. Patients are not stupid. They know that opioids have risk. They're not helpful for everyone. And I think if you come out, you have to present this very honestly, that opioids are good. This is how you should use them. You can help a lot of people. But not everyone should be on opioids.

MALE SPEAKER: So it's like an algorithm or something?

MALE SPEAKER: Yeah. And you could basically make a distinction between (inaudible). Right. There's lots of ways to do this. People have come up with all of these risk stratifications. So there are patients who are bad candidates because of their risk factors. There are people who are bad candidates because they may not have a condition that's amenable to opioid therapy, like people with pain all over their body or people with fibromyalgia. And I think that when you make this content, that you have to be really honest about it. And not all companies are honest about these things.

JOHN PEPPIN, DO: Just as a point, I don't know of any really good data that's looked at fibromyalgia and opiates, by the way, and showed that they haven't been

effective. That tends to be more of a myth than anything else. Not that I put my fibromyalgia patients on opiates.

STEVEN P. COHEN, MD: No, I mean, there are people with chronic abdominal pain. But I think there's a strong consensus that opioids are probably more harmful than helpful in people with irritable bowel syndrome. There's a lot of these things. Fibromyalgia there's no evidence to support it, and we know that these people have maybe increased risk. They all have sleep problems.

Opioids can definitely affect sleep architecture. A lot of them are depressed. They have social problems. These things have to be addressed. It may be that some people are helped, but I don't think the evidence is in support of chronic opioid therapy in people with fibromyalgia and other conditions.

And I think this is the thing. Purdue Pharmaceuticals, they have a great product. I don't think the company is held in very high regard, and part of the reason for that is because I think that they tried to mislead people. Maybe I'm naive, and this is just the way things work. But you can be like the NFL and you can say, "Look, we have a great product, but we have a problem, and we're trying to address it." Or you can be like tobacco companies.

JOHN PEPPIN, DO: So is that the choice you're

talking about?

MALE SPEAKER: Don't try to bury it in the beginning.

MALE SPEAKER: Right, right.

HOWARD A. HEIT, MD, FACP, FASAM: Everything is a spectrum of what we're doing. And so the question that's coming up is could there be some way that we could say an algorithm of what problems opioids would address in most of the people, some of the people, very little of the people, so that they know sort of like the risk management as far as the percentages of what we know which are opioid responsive. In other words, back pain, will that be responsive? Neuropathic pain? Less responsive.

Fibromyalgia? Who knows? So somebody could make a judgment of whether opioids are in the patient's best interest and give the doctor realistic expectations of what they should expect out of the medication. And you know this, doctors don't know the risk factors as far as addiction, physical abuse, sexual abuse. What questions should every doctor ask. Forget about doctors. What questions should every health care provider who could prescribe should ask before he or she places the person on an opioid. And I think that would by very, very valuable. And what should they do on the follow-up? And what role does urine drug testing play? I mean, give this thing.

STEVEN P. COHEN, MD: It's a great idea. Maybe you can put data into a computer, you know, age, demographics, these psych problems, this medical problem, this history. And then it can come out, "Great candidate."

JOHN PEPPIN, DO: That was Marty's idea.

MALE SPEAKER: "Poor candidate" whatever.

MALE SPEAKER: And you can set your boundaries accordingly.

MALE SPEAKER: Yeah. It would be very nice if life could be that simple.

JOHN PEPPIN, DO: Marty's idea with the stops on the electronic medical record. You come back, "Progress note. This is what you should be asking." Chris.

CHRIS HERNDON, PharmD: I think one of the things that would be beneficial at least from what I'm seeing in the smaller family medicine and primary care realms is that if we could come up with some type of package or Endo could offer this to some of these offices that has basically a step by step how do you put this together, almost like a chronic disease management toolbox that's ready to go, ready to implement. Draft policies and procedures for your clinic: Here's what potentially all of your different office staff can contribute, whether it's documenting in some way that your front office staff, you know, the appointment folks, their communications with the patients and how they might be

involved; the nursing staff; the MAs, who's doing these risk stratifications. So that when you go in as a primary care provider, which it's an NP or a physician, and you have your ten-minute appointment, all these things are well and good.

And I think that all the ideas that have been shared today are important, but it all boils down to you've got ten minutes a patient that needs an hour-long appointment. And what can we do to set the front line practitioners up with the tools that they need, not develop another tool necessarily, but here's your lunch box and you open it up and everything is ready to go.

Here's the recommendations for what this office person does, this provider does, so that at the end of the day you have some set recommendations on feeling more comfortable about doing this. Because I get a lot of phone calls even as a pharmacist, not as a physician, to come and help four and five physician practices set up policies and drug screening policies. They're trying to do the right thing. They don't know how to do it. They don't know where to get the information from. And they need someone, maybe even like part toolbox, part mentorship program where someone like you might come in and say, "This is how you do urine drug screening and risk stratification and those things." Does that make sense what I'm alluding to?

ROB GATLEY, MD: Are you familiar with the Andrea

Furlan's work at the University of Toronto with the Opioid Manager.

CHRIS HERNDON, PharmD: Mm-hm.

ROB GATLEY, MD: That originally was a paper in a published toolbox, like you're discussing. They just developed it as an app, so that again gets into the question of access and rapidly providing these things. It's something that might be included in an EMR.

MALE SPEAKER: We have a lot of those things on these websites already, where we've got all these different risk tools, but we really don't know which one is the best one and how to interpret them sometimes and all these different things. But I'm almost talking like, I don't know. I guess I'm not spitting it out.

MATTHEW S. WIEMAN, MD: Let me see if I'm on track here because I'm liking what you're saying. My analogy is like a central line kit. So if I'm going to go do a central line, the kit's there. I mean, there's lots of parts to it, too. There's physical parts and non-physical parts. But as simple as literally there's a kit. You open it up. Everything I need to do a central line is there. And it's reminding me, I've got to do this. I have to do that. I have to do this next. So I really like the conversation I'm hearing. I like the idea of the stop system, the system that says, "Stop." Now, I know this is going to be an issue for

almost everybody. It's going to take a little bit more time. But over time, it's forcing you to do this.

And then to your point about there are so many things out there, I think one of the things we have to do is to create at least a basic plan and start down that path because if you don't go down that path, there are so many different tools, different options for each of these levels.

And if we come to some consensus on this is a generally good one with some generally good background, and have that system in place and you do this, you do this, you can't do this until you go to the next step, in combination with something like that app, where again not everyone's going to have access to this, but perhaps you have certain patients that you want to have this app on. And then potentially, like you'd say, you don't get much time in the office, but they come in and they'll already have put a bunch of information on this, and it'll kind of cue you to have that discussion, as well.

And one other thing about that which is kind of exciting to think about is you could really tailor that app to that patient. So listen, everybody who gets a script, here's my little packet. Here's an agreement. You're going to see a counselor at least once. You're going to come in for urine drug screening every month for at least the first few months. I do this to everybody across the board. And

then with the app, something along the lines of you'd be able to tailor it. So, you know what? This patient doesn't need to tell me every five minutes how they're doing. This one does, so I'm going to turn on that feature. OR this one I want to see. You know, record your pain score and tell me what you're doing right now. Heck, it could even tell you if they're active, if the person's moving.

M. CARY REID, MD, PHD: I'd just say the assessment piece absolutely has to move outside the clinical venue, given the time constraints. And I think the telehealth mechanism would allow for that. So there would be this sense that the patient had to enter the data before coming back, and those data were ready to be looked at by the clinician. So that makes a lot of sense. I think it's a win-win.

MARTIN D. CHEATLE, PhD: What we do in the pain clinic is they can do it online, but before they are seen by anybody they have to fill out. They go to a kiosk. They have to put in changes in medications. They have to fill out a PHQ-9 for depression. They have to put their pain scores. That's all sort of fed into the computer, so when the attending or the resident comes in, they pull it up and it shows what the depression rating is, what this is.

And I think you have to build in other things, like pain contracts. So you have someone fill out an opioid contract on day one. I guarantee you 95 percent of

practitioners never look at that again, and so those are little things you have to build in. You have to look at that six months from now. Pain contracts are based on goals. I'm giving you an opiate, I'm giving you an antibiotic for this goal. We're six months into therapy, and we haven't achieved any of the goals. Maybe opiates aren't the best thing. I think that's what Steve is saying.

You would take a step forward by saying that opioids aren't good for everybody and that here are some measures that if you start someone on an opiate and three months into it we haven't achieved any of the therapeutic goals, you need to rethink that this isn't the right molecule for you. Or you have a PHQ-9 score that shows that you're severely depressed, but I didn't send him for psychiatric care, I didn't change anything.

So people collect all the data. I'm not sure they act on it. That's why you build it into the stop measures. If someone has a PHQ-9 higher than this, you have to do something. Because they won't think about it because they're five patients behind. I have seven minutes, and I have six phone calls to answer. So it has to be, "Keep it simple, Stupid." KISS. It has to be very easy to do or they won't do it.

GAVRIL W. PASTERNAK, MD, PHD: I really want to emphasize that, and I get a little antsy when I hear about

you have to do this before you can go to the next step, and you have to do this. What's happening, and our place I don't think is any different from anybody else, okay, well we really want this information. It's only 30 seconds extra for a patient. That doesn't sound like a whole lot, but when you have a clinic of 20 to 30 people, by the end of the day you're finding that they're just not doing it.

So you have to make it so that it's actually going to save them time and not cost them time. It's so easy. And you have to understand that you're not the only one making these demands on people's time. Everyone's going to be doing this, whether they're treating heart disease, whether they're treating something else. Everyone's going to have these paradigms.

And as they start to expand because we think they're so wonderful, the constraints on time are going to be such that people -- I mean, our medical records system at our place is wonderful. It's all electronic, and it drives you crazy. It takes me twice a s long to get a patient out of the office room than it does if I were to write it down, write the prescription by hand, and send them out. At some point it falls apart. Twenty years ago we had these really great disease management systems, and the argument was "It's only 30 seconds a patient to put them in here. We can get all the data back. We can keep track of patients with

different diagnoses." No one did it.

MARTIN D. CHEATLE, PhD: You know what we did with primary care docs is I implemented a system that rather than pain as one of their presenting symptoms, that's what the problem is. And you put every so many months if you're on opiates, you're going to have an office visit that's just devoted to pain. So what happens, they go to the primary care doc, and they said, "I got this lump here. Oh, by the way, my pain's out of control. I need more opiates. My high blood pressure."

So we got them to like every three months or six months to actually just have a pain-focused assessment so it wasn't as complex as that. It wasn't just one of the problem lists. And that really helped them actually because they were able to really focus in just on the pain.

M. CARY REID, MD, PHD: But the unanswered question is what will adherence be like. And if you build a complex that adherence has got to be low in interacting with the device. We've talked about the way that the device could potentially help the patient, might help the provider. There's another way that it could help, and that is imagine 1,000 people or 10,000 people on Opana all using a device generating information. What it could do is provide benchmarks for age groups and diagnoses. And so instead of just having your own data, now you kind of see where your

pain and function is relative to people who are 50 to 55 with back pain.

MALE SPEAKER: National registry.

MALE SPEAKER: Yeah. And so it literally could operate that way if you built it.

GAVRIL W. PASTERNAK, MD, PHD: (inaudible) about privacy issues.

MALE SPEAKER: Yeah, it's a huge issue.

GAVRIL W. PASTERNAK, MD, PHD: And that's a real issue. We always talk, we talk more about privacy today and keeping it, and we do less about it than ever before. And especially with the electronic medical records. I mean, anybody in our place that has access to the records can look up anybody. After the fact, someone can come back and slap their hands and say, "You weren't supposed to look at that record." But I tell you, a lot of people don't like that.

ROB GATLEY, MD: There are a lot of holes and things in EMR today that are not very user-friendly for that situation. There's no reason why the EMR couldn't keep track of who looked at what.

MALE SPEAKER: Oh, it does.

MALE SPEAKER: Then they could be held responsible later.

GAVRIL W. PASTERNAK, MD, PHD: No, it does, but it's an after-the-fact. Because if someone comes in to our

equivalent of an emergency room, if you have a prior authorization, you may have people have to take care of a patient that can't access the records. So everybody can access it, and they keep very close track. And after the fact if they find someone was looking at a record they shouldn't have, they come back and they slap your hand. And we've had people fired for that. But that's kind of the barn door and the horse is gone type of thing.

JOHN PEPPIN, DO: (inaudible) point that there is the incentivation [?] of spending time, and a badly managed patient can take up a lot of time. And there's pharmacoeconomic evidence that patients with substance abuse problems cost nine times more than a compliant patient because of the extra time, the doctor-shopping, the degree of care they need. So these tools might document that, that investing the time in proper counseling actually ends up in an economic saving. That would be evident from the database. So I think we have a great discussion on this topic. And we're going to try and keep to the schedule, because we're now at 9:30.

[FILE 2]

JOHN PEPPIN, DO: So I'd like to introduce Chris Herndon from Southern Illinois University. And I'd like to announce he's had a promotion, so our slide is not accurate. You're associate professor now? Good. So we'll let Chris

talk about the molecule.

Oxymorphone Pharmacology

CHRIS HERNDON, PharmD: Thank you for having me. I have to admit this is a little nerve-wracking. Giving a talk on opioid pharmacology with Dr. Pasternak in the audience is like giving a talk on chicken to Colonel Sanders. [Laughter]

GAVRIL W. PASTERNAK, MD, PhD: Well, he had a nice white moustache, too. [Laughter]

CHRIS HERNDON, PharmD: And we do have a colonel in the audience.

MALE SPEAKER: Sho'nuf.

CHRIS HERNDON, PharmD: Oxymorphone from a pharmacologic standpoint is really an interesting molecule. It's a pure semisynthetic opioid. It is relatively selective for the mu opioid receptor until you start getting up into higher doses, and then you start to see a little bit of delta activity as well. Some interesting things that are noted on this slide. One, that patients that are over the age of 65, so some of our older population, do require lower doses. They tend to have a correspondingly different AUC.

The half-life of the medication for the IV formulation is about 1 1/2 hours. The IR formulation is around seven. And comparatively to some of the other typical IR opioids that we use, this is a little bit longer than

what we would see with our hydrocodone and morphine products, as well. The ER formulation is right around 12 hours from an half-life standpoint.

And the other thing I want to stress here, too, is that as we're going through these slides, I've been asked to share with you all to be thinking about while this is the information that's in the prescribing information for the product, be thinking about does any of this jump out to you, does any of this say, "Wow, this is something that's really going to change the way I feel about this medication," or "We need to be telling prescribers or providers about this particular information." So please keep that in mind.

From a metabolism standpoint, one of the things that is a little bit interesting about oxymorphone is that it is considered an active metabolite of oxycodone. It goes through further metabolism via glucuronidation to both inactive and what we think to be an active metabolite, which is the 6-hydroxy glucuronide. The bioavailability of the drug does increase in both renal as well as hepatic insufficiency. Correspondingly as you go from mild, moderate to severe, the bioavailability will go up, as well as the AUC.

The other thing that's interesting here, too, is that as far as we know, the sole metabolic pathway for oxymorphone down to these two glucuronides is through the

UGT2B7, so it's a relatively clear metabolic pathway. It doesn't have a number of different metabolic pathways like some of the other opioids that we deal with. And this may have ramifications from a testing standpoint.

So I know we real briefly touched on urine drug screening. That in and of itself is an art I think, interpreting some of the results that we get from those. This is probably one of the things I'm asked about most frequently is "What does this mean? And what do we do with these results?" In most of the urine drug screens that we have available to us today, I think having the oxymorphone as one of the results in your urine drug screen makes interpretation a little bit easier because we're not dealing with a number of different metabolites that could be from a drug in and of itself or from a parent drug that the patient might also be taking. So keep that in mind, too. Does this resonate with people as far as being something that is potential important or not?

From a kinetic standpoint, most of our other opioids do get metabolized via the cytochrome P450 2D6 system, with the exception of hydromorphone and morphine. My understanding is, is that from a clinically significant standpoint, we have tramadol, which has to be metabolized via 2D6 to its O-desmethyl metabolite to get significant analgesic activity, as well as codeine. With oxycodone, we

see 2D6 and 3A4 metabolism. We don't think that inhibition of those metabolites or the lack of those enzymes necessarily reduces analgesic activity, but can increase exposure and potential toxicity of the drug. And then we also have fentanyl, which goes through 3A4, which can be a significant drug interaction.

Unfortunately I've got some personal experience in our practice with somebody getting hurt via that drug interaction. So keep that in mind as you look at this. And the CYP system and oxymorphone's lack of going through this system, and also the consideration that most of our chronic pain patients that we may be considering a sustained-release or a long-acting opioid formulation likely have other comorbid psychiatric conditions that may add a whole host of potential drug interactions to the mix.

As far as opening up this discussion, I know that there's been a lot of different publications that have come out within the last year or so regarding safety of opioids. When I went through school, we were talking about education, I was always taught that as long as you titrated the drug correctly and the patient became tolerant to the respiratory depressant effects, the sky was the limit. You could go up as high as you wanted to, and there was no danger to doing that. And so I think now we may be starting to question that practice a little bit and we're not really sure potentially

why that is the case that we start to see this increase in risk of opioids at higher doses. But that is becoming quickly a discussion that's occurring both in circles of professionals, as well as circles of legislators. And so I think it's something that we need to add to the discussion.

If you go through and you look at some of the adverse effect data that's been done with oxymorphone, based on this slide we see that we actually tend to see a fairly good tolerability with the drug as we go up to some of the higher doses. Some of the actual studies that may not be referenced on this particular slide do show adverse effect dropouts in some of the clinical trials to not be significantly different as you do go up and when the titration occurred appropriately.

And interestingly when you do get to the higher doses of this particular drug, the adverse effects that you see may not be necessarily what you would expect: i.e., in the oxymorphone ER particular drug you start to see increases in anxiety, pyrexia, and upper respiratory tract infections. And I'm not sure if the increase in anxiety may be a change in the opioid receptor selectivity as you start to see higher doses or not. I'd be open to hear your commentary on that.

This is the slide that I found to be probably the most interesting. When looking at oxymorphone compared to

some of the other opioids, specifically oxycodone, and looking at likability, for lack of better terminology, they basically take healthy individuals and expose them to the medication and then "Which of these would you like to have in your hand again?" And I can't imagine how these get passed through IRB, or where do I sign up for a study like this.

MALE SPEAKER: You want to know where to sign up? Ed Sellers'[sp?] group goes around to the bars on Queens Street West in Toronto at closing time and tries to solicit people to volunteer.

CHRIS HERNDON, PharmD: Really?

MALE SPEAKER: Yes.

CHRIS HERNDON, PharmD: Okay. Well, you guys need to come to St. Louis. And this positive subjective effect, they have a number of different tools that they use where they'll expose patients to these types of medications, and whether they just say, "Hey, did you like it? Ring the bell if you want it again," kind of thing versus some very nice outcome measures where they'll look at these questionnaires and actually I think the FDA uses some of those different types of questionnaires to determine the controlled substance class that they put one of these medications in.

So anyway, the study of healthy volunteers found that basically the people who we really don't want liking

oxymorphone like it less than controlled-release oxycodone. So that's actually good news. The other thing that's important from a psychomotor standpoint with oxymorphone is that we tend to see a lower psychomotor effect with oxymorphone as you titrate up. And that has significant effects both in risk of falls -- I'd like your input on that, as well -- and also some of the things we typically get worried about: Are you going to leave on this medication and go operate a forklift or drive home or whatever it might be, that we have to have some of those conversations with our patients. And you all, I think everyone in the audience probably is very familiar with some of the changes that have occurred with some of these products and their release, their ability to be tampered with, et cetera. And so those are some things that I'd like to pull out as we go into this portion of the advisory board, as well.

So, how was that for a fast and furious? [Laughter] Is there anything that I said from statements off of what we know about oxymorphone, extended-release oxymorphone that you all feel strongly about, either positively or negatively, that you would like to share? Or is this how you want this to go? [Laughter]

MATTHEW WIEMAN, MD: What do these things matter to you? Do they matter, and if so, why? Is there enough information about them? To some of you, you may not be

focused on that, one of these bullets up here.

HOWARD A. HEIT, MD, FACP, FASAM: I think it's extremely important for the company to teach the strengths and limitations, I would say not screening, but urine drug testing, and especially with costs being a fact, that strengths and limitations of point-of-care testing because somebody could use point-of-care testing that's done by immunoassay, and the person is on Opana and come back negative because the point-of-care wasn't directed towards that particular molecule. I know they're getting more sophisticated. So one of the things is education about the strengths and limitations and interpretation of urine drug testing and opioid metabolism.

MATTHEW WIEMAN, MD: Anybody else have comments on urine drug testing and metabolism?

CHRIS HERNDON, PharmD: I think it's a very important component, especially in the primary care world because we'll see people that will make treatment decisions based off of those cups and cartridges.

HOWARD A. HEIT, MD, FACP, FASAM: Right. The semisynthetics are reliably unreliable.

CHRIS HERNDON, PharmD: Right.

ROB GATLEY, MD: I think it's a key point with that, too, Howard, because OxyContin crush-resistant came in before Opana crush-resistant. So there was a period of time

where people were being put on the crush-resistant OxyContin and going and stealing or buying Opana. So a question some prescribers have had is, "I gave this patient the crush-resistant OxyContin. How can I tell if they're abusing Opana that they bought on the street?" You can't really, can you? Because both show oxymorphone in the urine.

HOWARD A. HEIT, MD, FACP, FASAM: Other than the possibility the ratio of the parent drug should be higher than the metabolite. But again, it's where you capture them as far as the urine specimen and when it was donated.

ROB GATLEY, MD: So does the average prescriber have any idea of how they'd approach that?

HOWARD A. HEIT, MD, FACP, FASAM: The average prescriber doesn't do urine drug testing.

CHRIS HERNDON, PharmD: I guess my input would be we see these nice reviews like on Medscape, and I know I've read some of your work about how to interpret urine drug screening and what to do and when to do it and how often and those things. I mean, if you're looking for recommendations on things Endo can bring to the table, I would like to see something where I can go with all of the major labs and tools that are available, not the overview of here's what GCMS is, here's what immunoassay is."

But if I order this test from LabCorp or if I use this cup from company C or whatever, all of that information

in one place so that it really is a guide on how to do this with the results. Because an opiate screen from my hospital lab will only pick up morphine and codeine, but if you look at the LabCorp opiate screen, it picks up hydrocodone, morphine and codeine, but not oxycodone. I mean, there's no rhyme or reason to any of them in the way that the name them.

MALE SPEAKER: That's why you have to know whoever your vendor is, is to be able to speak to either the vendor or the lab in order to again know the strengths or weaknesses of the test you're ordering if you're ordering the test.

ROB GATLEY, MD: That's of interest to Endo as well, because they have an arm that does monitoring, that develops the equipment for monitoring the tests. And I think in terms of when I was in practice and ordering urine tests, I was filling out a form, sending it off, maybe I could try and get someone on the phone for a question. But I think in this day and age, there could be online access through whoever's doing your testing to ask that kind of question, that 90 percent of the time could probably just be answered electronically through a help function: What kind of test do I order? What should I expect to see back?

RONALD J. TALLARIDA, PHD: Your last statement, are there aspects of oxymorphone requiring further research. Has

there been any interest within the company for looking at combinations of that with other drugs? Tramadol we combine with acetaminophen. Tapentadol has a built-in, intrinsic dual mechanism. Even ibuprofen has enhanced efficacy when glucosamine is added. Is that anything within the company's interest?

MATTHEW WIEMAN, MD: That is something, the combination, that's one of the ideas for where we could go with the molecule in the future. And there's a lot of questions to that. So some of them are, you know, do we go down some other route, like MoxDuo, so to capitalize on some of that synergistic effect between kappa and mu or delta and mu, if I'm not mistaken. And this is the question I'd throw back t you, so there is interest. And then some of that gets down to something like a combination of acetaminophen and oxymorphone.

I think there's a little bit more issues that would come with that, given the recent push around reducing the use of short-acting, the use of anything containing something else, like acetaminophen. However, there are lots of other ideas, too, to turn to, to use this. So what are your thoughts on combination? I know you have quite a bit of experience in that now.

RONALD J. TALLARIDA, PHD: We have a lot of experience with let's say tramadol with gabapentin and other

agents that are anticonvulsants. We certainly don't understand the pharmacology of why that's so, but we have remarkable synergies between these. And because this agent, as we're all in agreement, has its adverse effects prominent at higher doses, if you can find a combination with some other agent that reduces the dose, chances are that will not only be helpful in the treatment, but it also might allay some of the fears and concerns physicians have. I think a lower dose opioid would be less concerning by the physician, based on what we've been discussing this morning.

MATTHEW WIEMAN, MD: I actually have a question about that, too. So something like Nucynta, what are your feelings on having a drug like that that's a combination, multiple mechanism of action? There may be certainly a group of patients that it just works perfectly for. Coming from the anesthesia background, it's really always easier for me to say "I'm giving this for this, and I'm giving this amount. And if I need to adjust it I can."

But I hear a lot of the benefit. We see the benefit. It's approved. They have indication. How do you feel about or does anybody have any strong opinion on the ups and downs of providing a drug that you can't change that. You've given that. And if the person has pain relief, is it the gabapentin or is it the oxymorphone? If they're having an adverse reaction, which one is doing it? Is there

a concern around the negative side of that, as well?

RONALD J. TALLARIDA, PHD: Well, I think the formulation of any combination, anything you're going to put in a patient has to certainly be tested first preclinically. And all good things that patients ever get always began with preclinical investigation. So we would have that kind of information available.

MATTHEW WIEMAN, MD: So we would go down this path. How much would that impact your practice? And again, we're at the very beginning, but is there a number of patients you say there's more than just a few that I could really use this type of product for?

HOWARD A. HEIT, MD, FACP, FASAM: I think for the general practitioner, it would make it more complex because you're adding another variable into the system in which they haven't mastered the basics yet. So I think of all the paths that the company should go down, that would be an expensive path, a lot of research would have to be done, et cetera, et cetera, getting it through the system, the FDA approval, Phase I, whatever. I think your efforts should be placed on it's complicated enough without introducing another variable.

RONALD J. TALLARIDA, PHD: I don't think there's anything more complicated about putting together let's say acetaminophen with tramadol than there is in looking at the

side profile of this oxymorphone and all the metabolites that come from it. Why do you think that's more complicated?

HOWARD A. HEIT, MD, FACP, FASAM: Because then you're introducing the other variable of acetaminophen, liver dysfunction, liver abnormalities and all the other products.

RONALD J. TALLARIDA, PHD: Oh, I'm not saying you have to consider only acetaminophen. There are a variety of other agents. Take tapentadol. Intrinsically it works. It is probably better than tramadol because it combines two mechanisms of action. And if you can combine this drug here, oxymorphone, with something, there's at least the theory. When a physician is concerned about whether or not the combination dose is appropriate, that's a reasonable concern.

But the assumption is that the physician practicing and making that adjustment knows more than the whole body of research that produced it. I don't think that's true. I'd be more inclined to trust a combination of acetaminophen and tramadol than what any individual physician might try to do to correct an abnormality.

GAVRIL W. PASTERNAK, MD, PhD: I just have a couple of comments. First of all, it's my experience it is extraordinarily rare to see anybody manage a patient in pain with one agent. We can start from there. Because what

generally happens is you start with drug number one. Not so great. You add drug number two to drug number one, or you use a combination product. So I think the concept of combining drugs is the norm rather than the exception. Number two, I think for simplicity's sake, it's easier for the people who are not necessarily experts to give a single agent. It's easier for the patient to take one pill. And particularly if you start adjusting doses, if you have two pills, "Well, today we want you to take one green pill and two red pills, and tomorrow we're going to have you take two green pills and two red pills," it gets to the compliance of the patient is very difficult.

On the other hand, the combinations, we talk again about this homogeneous population of our patients. And again, you can argue about how easy it is to extrapolate from animal models to people, but I can show you that a lot of these interactions that we're able to see, the interactions for example between some of the NSAIDs and opiates, are very much dependent upon the strain of mouse that you test them in. Not every strain of mouse shows you the same effects. So that I think that when you're dealing with your patients, you have to understand that there's no guarantee that what works in patient A is necessarily going to work in patient B.

This is one of the problems I see in terms of pain

management. We're not looking like an antibiotic where you're treating an organism that you can isolate and is identical from patient to patient because you're going to only work with the pneumococcus. You're dealing with very subjective things, that people have genetic backgrounds that alter the overall effect of this. Not everyone feels pain the same way. Not everyone has the same reaction to pain. Not everyone has the same reaction to opiates.

Finally, one of the problems whether we talk about education is that the biggest problem in education, the most intransient problem in education where the feet are stuck in the sand the hardest, the FDA. And you talk about combinations. Try dealing with the FDA. We're not talking science. We're not talking about medicine. You put together two opiates and the FDA doesn't get it, even though we know there are situations where they can be very effective together, more so than each individual one alone. So getting back to Howard's point, I mean the FDA is going to be a major factor in this, despite all the science and all the good clinical observations that you have.

MALE SPEAKER: (inaudible)

GAVRIL W. PASTERNAK, MD, PhD: Well, the FDA, they have never gotten a kick in the shin for not approving a drug. I mean, any time you approve a drug, it's a risk to them. And so you take the most recent one, which is

hydrocodone, I think, someone corrected me last night, long-acting. And the advisory board turned it down, not because it didn't work: because they were afraid you'd sell too much opiate. At least that's what the news report said. So I think the regulatory agencies here.

And this is a pendulum that goes back and forth. We're back to where we were in the '80s. And then there was the pendulum went the other way and everyone was giving opiates because we were supposed to be compassionate and nice. And now we've turned mean again. [Laughter] And we go in the other direction. And the DEA is running our no pain policy in this country at this point. There's a palpable fear among practitioners that they're going to get records audited by the DEA. I mean, even if it's not realistic, there's that fear. So the politics of this thing I think is going to have to be also very important.

HOWARD A. HEIT, MD, FACP, FASAM: So you want to determine as a company what you want to accomplish next week, next month or three years from now and what is your objective.

MATTHEW WIEMAN, MD: Right now I think their objective is long term, with every plan in between. So we have some running room, and our goal is to maximize what we can do with the molecule, oxymorphone ER specifically in this case, but hopefully it just makes sense, again, we'll

get into continuum of care next, to have them all out there. So we will have plans that we'd like to do studies that are done this year to be able to show something. And then of course some of these other ones that are some great ideas like potentially using that system to catch a natural registry of all of our use and see what it's good in, what it's not, would be longer term.

CHRIS HERNDON, PharmD: So let me ask you all, coming back to some of the points that I was interested in, when we start talking about differences at opioid receptor types does that resonate with anybody from a clinical standpoint? Does anybody care?

GAVRIL W. PASTERNAK, MD, PhD: I do.

CHRIS HERNDON, PharmD: What does it mean to you?

GAVRIL W. PASTERNAK, MD, PhD: I may be the only person. I think it's an area that really is just not appreciated. The science for many people is just too deep. I can tell you that the traditional mu receptor, for example, between mice, rats and humans that we have over 50 different subtypes. And yet all these drugs are working at these receptors and nobody cares. And the FDA is classic on this. There's always a bit of inertia turning the Queen Mary. You can turn the wheel as fast as you want to, but it's going to take a long time for that boat to make that turn.

And I think that's where we are there. It helps to

explain some of the observations that we've known about for decades: that not every patient responds equally well to each drug, and that their relative potencies vary. But getting that to the point where the regulatory agencies appreciate that and can understand that maybe a company of two opiates is not giving the same drug twice. That may be a little time coming.

RONALD J. TALLARIDA, PHD: (inaudible) response to that question. A big concern of course with opioid preparation has been the gastrointestinal inhibition. There's constipation. And so there's always been interest in finding more specific opioid receptor types, like a kappa receptor that might produce a degree of analgesia without as much of that adverse effects. So that's another reason why. His is kind of research produces information of that kind.

GAVRIL W. PASTERNAK, MD, PhD: Can I quote that and send it to my father? [Laughter]

STEVEN P. COHEN, MD: I wanted to make one more point about combination therapy before. Like I said, I deal with the government in a lot of -- and I can tell you at least from the perspective of like opioids, they basically operate from a risk mitigation perspective. So every protocol that the Walter Reed IRB approves has the potential to cause harm. So it's a very different goal for a Johns Hopkins. They want to approve many particles. It brings

money into the institution. It brings prestige. Walter Reed, it can just create problems.

And it's not like you're approving a cancer drug. If you combine oxymorphone with acetaminophen, it's not like you're approving a drug where there's no niche. I mean, there's already many, many products. This is going to be the twelfth or the thirteenth or the fourteenth. And it may be very difficult. I mean, you had a lot of people voting to actually get rid of all these combination products together with the opioids and acetaminophen.

And I'm not as much of an expert in this as someone like Dr. Pasternak. But there's definitely evidence in preclinical models of combining like gabapentin with opioids maybe to reduce tolerance. And then there is of course the article by the Canadian group, Gilron. And this is something for neuropathic pain, that hasn't been really looked at, but that I think there is maybe better evidence that it could work, and there's no other product there. I mean, you have an individual niche.

And so instead of just trying to take the road that ten other companies have already taken and put oxymorphone with acetaminophen and then have to compete with Vicodin and Percocet and a lot of other companies, and then have to go through the travails with the FDA and there's a really good chance that they wouldn't approve another one,

because why would they.

RONALD J. TALLARIDA, PHD: Well, here's why they would. Synergism, which is desirable from the point of view of its therapeutic effect, is a property not only of the two drugs, but it depends on the ratio of the two. Consequently, if one could take the combination quantities such that you're synergizing the desired effect but minimizing the undesirable effect, then you have something very different.

STEVEN P. COHEN, MD: I mean, rational polypharmacy people always talk about it. I think it's great conceptually. I think practically it's very difficult. And I think like I say, you're also dealing with the FDA. They're not always experts. And then you have many competitors. But I think that there's pretty good evidence for combining oxymorphone. And I think the risk is probably lower. Gabapentin is really safe. People think you should stick it in the water supply. And I think that there's enough --

MARTIN D. CHEATLE, PhD: That's Cymbalta you put in the water supply.

STEVEN P. COHEN, MD: Cymbalta may be better.

MALE SPEAKER: Use some Prozac for that.

STEVEN P. COHEN, MD: But I think that you might kind of consider looking outside of the box here when you're considering combination therapy.

GAVRIL W. PASTERNAK, MD, PhD: With the animal

models that Ron and I use, you can really well control those, and you have homogeneous populations. And you really can do very rigorous types of studies of synergy. I'd be interested in what Ron has to say. Because my understanding, and I could be wrong, is that demonstrating synergy in a clinical population is not very simple, and it's not really been easily done. And at the FDA, if you apply synergy to the FDA, then you actually have to show it. And I was curious what you think about doing the clinical trial.

RONALD J. TALLARIDA, PhD: When we worked with the tramadol/acetaminophen thing, that was still a very, very new experience for me. And we tried so many different fixed ratio combinations, and our patent was sufficiently broad that it was first patented for just about all kinds, for one-to-nine to one-to-one. And then when the clinical people decided to start designing the clinical trials, the question arose, "What should they try?" And what we did was got something that we knew would be synergistic, but at the same time would not enhance any of the adverse effects. And maybe we were lucky, but that produced the drug called Ultracet, which is now being sold everywhere around the world. Maybe it was luck. But we had to do a pharmacokinetic profile, of course, because it's a lot different. As Gav said, we can control the amount in a laboratory animal, but then when you get into a patient, based upon the pharmacokinetic profile,

the drug's peaking at different times. We had to work that out. But it was like a math problem.

STEVEN P. COHEN, MD: I think that's actually a great product. I think tramadol is a little bit different than oxymorphone. It has a different potential for abuse. It's in a different schedule. Definitely I believe that opioids have a ceiling effect that relates to their adverse effects. But I think that the ceiling effect for tramadol is lower, and so I think that's a great product. I think that there's more competitors here. I mean, Percocet is generic. There's all products with hydrocodone. There's a lot of other things. I think, "Look at this. It'll be okay." But I think it's going to be harder to get approved. it's really difficult to do a trial like Gilron did with morphine and gabapentin. And look, I know these things are nightmares, but it can be done. And I think that they would be more amenable to something completely new with a niche that would actually lower the risks associated with opioids.

JOHN PEPPIN, DO: That was a pilot study.

MALE SPEAKER: I'm sorry, what?

JOHN PEPPIN, DO: That was a pilot study.

MALE SPEAKER: Gilron?

MALE SPEAKER: In *New England Journal*, yeah. You're talking about expanding it way beyond that is my point. Yeah, that was difficult. Just doing the pilot was

difficult.

STEVEN P. COHEN, MD: Like I said, I'm not saying that good things are easy to get in life. I mean, you have to work for them. That's it. I'm saying that it's definitely something that's doable, and I think it would be something that would garner more interest than combining another opioid with acetaminophen again.

MATTHEW WIEMAN, MD: Well, I'm hearing a lot of risks and benefits, but interest in the potential for this. So I think this opened up a good conversation. I think we can look into what are the next steps from here. Obviously it is something that might be beneficial.

RONALD J. TALLARIDA, PHD: Just one interesting thing. I never intended to get as active in the field of drug combinations as I did, but I'll tell you, if I could just amplify. About 20 years ago or so, I was somewhere, I think it was consulting for Procter & Gamble, and at dinner that evening the host person said, "By the way, you're not here for this, but would you tell me how do you combine so many milligrams of drug A and so many milligrams of drug B?" Well, because this was dinner and I'd had wine, I said, "I'll do that tomorrow." I didn't want to try to do any computation.

Well, I found out the next morning when I had no wine in me, that I still didn't know how to do it. And that

motivated me to get interested. And until today, this is still true and it's still surprising. There is no textbook in the world that tells you how to do the following: Given dose A of drug A and B of drug B, what is the expected effect of the combination? That should be on page 7 of everybody's book, but no pharmacology book in the world tells you that.

MALE SPEAKER: But you have a couple books.

MALE SPEAKER: Well, I did that. The only reason it sells is because nobody else cares about it I think.

GAVRIL W. PASTERNAK, MD, PHD: Well, I bought it.

MALE SPEAKER: You did! Good.

MATTHEW WIEMAN, MD: So this is all good information. Again, I think we've hit on that a little bit, which would open the door. One question. I wanted to go back to the receptors just really briefly. It combines the whole long term, short term, and medium plan, and so I would look for your opinion on something like that. Because you hit on the key. The key is, is it clinically meaningful at all? How close are we to any data that would matter to the people that are treating today? And so do you see with your knowledge any low-hanging fruit or angles or specific topics that may even open the door or be pilot studies or be more interesting and applicable to clinical practice sooner than later? Is there anything?

GAVRIL W. PASTERNAK, MD, PhD: I think that the clinical studies may be difficult to do. Obviously the best thing that you can do to push a product such as this is to show that it's distinguished and different in some way from at least some group of other, quote/unquote, new/old drugs. And that I think would be very helpful because then you can say, "Well, if you're having trouble with this group, you go to this group."

One of the things, and this is relatively low-hanging fruit, I don't know how familiar you are with the concept of knockout mice. These are mice where you genetically engineer them and you take out different parts of the gene.

And with a mu receptor, the mu receptor actually turns out to be extraordinarily complicated. It's about 250,000 base pairs long. And you can take out pieces and affect some set of these splice variants without affecting other sets. So for example, John Pintar[sp?] made an animal where he took out exon 1. Morphine is totally dead. Heroin still works. Morphine 6-glucuronide still works. Some compounds we've synthesized work.

We made a different knockout where we took to exon 11. The numbers don't matter. But in that knockout, which also affects the mu receptor, morphine works fine. So does methadone. But you find very dramatic shifts in the

analgesic activity of drugs like heroin M6G. And some of our compounds that show absolutely no cross-tolerance to morphine and show no respiratory depression, they're dead. Ironically if you take that exon 11 knockout and you test compounds like levorphanol -- many people around here don't know levorphanol. But it was a Hoffmann-LaRoche drug. We use it a lot because I think it's a great drug. That was impaired. And you know what other compound was totally dead in that group? Buprenorphine.

So here you have in a relatively simple model all based upon mu receptors groups of molecules that either requires one set of splice variants or another set of splice variants, and yet people have long considered all these just to be identical mu drugs. To my knowledge, oxymorphone has not been looked at in any of these.

MATTHEW WIEMAN, MD: Okay. To me that sounds really interesting because again we know that clinical studies may be a long way off to find the outcome. But as you say, it's really important for us to be able to say what is different about Opana ER. And if what we can say is that, then that's what we can say. So this is one of those avenues we may be able to go down to look at further studies.

And I wanted to bring it a little bit back in to Opana ER. So when you think about the drug itself, it really comes down to some of these more basic questions. We've hit

on a lot of them, but I've asked you to kind of rethink about is there a reason, a primary reason, aside from of course patient selection, setting, there's a lot of other factors. Are there any things, basics, about Opana ER why you use it in your practice? Anything specific? We mentioned some of the things about the metabolism. We mentioned its high lipophilicity. We know it has a longer half-life in some cases. We know that -- and whether this matters or not to you folks in your prescribing -- but the elderly require quite a bit of a less does. Those factors or any other factors or anecdotal information about how your patients react to this drug, why would you choose oxymorphone for your patients? Do you have specific types of patients that you do use it for?

JOHN PEPPIN, DO: You know, those questions are so complicated. I mean, how many times have we all been asked the same question from perhaps other companies. And I think about when a patient shows up in my office, I mean, what's their insurance going to cover. And that's a big issue, right?

MALE SPEAKER: When it gets out of the formulary.

HOWARD A. HEIT, MD, FACP, FASAM: Right, exactly. And so I may say "I wouldn't want to put this patient on morphine because they've had it before and they threw up, and it's a problem." But maybe that's all that their

insurance will cover, which is crazy. I don't know. It's a difficult question. Go ahead.

CHRIS HERNDON, PHARMD: I don't know that there's any data to support this, but I've noticed just in the folks that I've had on the long-acting formulation, there tends to be less dose creep. I don't know if that's the right word.

MALE SPEAKER: Maintain.

MALE SPEAKER: Right. But I tend to find that we're able to protect the current dose for --

HOWARD A. HEIT, MD, FACP, FASAM: (inaudible) pharmacologically and addiction-wise in its longer half-life?

MALE SPEAKER: I don't know. I'd throw that out to you all.

STEVEN P. COHEN, MD: I tried to look up this. I did my fellowship with Jean Min Mao[sp?], who is one of the guys, opioid hyperalgesia, and he used to tell me even when we were fellows, "Oh, medications with long half-lives, sustained-release formulations, less tolerance, less opioid hyperalgesia." He used to say this all the time. I thought it was gospel. And when you try to find it, I think it's very difficult to find. People say this a lot. It may be true. There may be evidence, but I don't think there's a lot of evidence for it, or if there is I don't know what it is to support that. So that's something that could be true.

GAVRIL W. PASTERNAK, MD, PhD: I think opioid hyperalgesia is a discussion for another time.

STEVEN P. COHEN, MD: Or tolerance. We're saying both of these things are reasons that people increase their medications. And I think that's what you were implying. And I think that this is one of the things that's said a lot. And I don't think in my opinion there's really strong evidence for that. It may be true. Like they say, the absence of evidence is not the same as (inaudible)

GAVRIL W. PASTERNAK, MD, PhD: I want to give an interesting observation. First of all, all of these drugs produce tolerance. They don't necessarily produce it at the same rate. So again, I don't know what the applicability of animal models to clinical models. But tolerance for example develops much more slowly to methadone than it does to morphine. And Brian Cox, who is down at the military medical school showed almost 50 years ago that if you infuse morphine into a rat you get marked morphine tolerance in eight hours. So tolerance is going to develop, but they do differ.

But what's extraordinary to me, and I'm just going to give you some guesstimate numbers, about 70 percent of patients will respond to almost any opioid that you start them with within the mu category. But there is this additional small population where you find that drug A is

much better than drug B, whether it's methadone versus morphine.

And I haven't used oxymorphone clinically enough to really tell you, but I would not be surprised if there are going to be small populations of patients who are going to respond better with that particular drug than the others. Obviously the drug that you start with that has the largest catch-all is going to be the one that the physician is going to like because they're going to have to switch drugs less often. Does that make sense to you?

MATTHEW WIEMAN, MD: Yeah, it does. That's kind of why I asked. If it was a perfect world and you had no limitations on formulary issues, and a patient comes in. And again, there's a multitude, I know. This is that same question again, but it's really part of this. That's why this is a minor part of the discussion. But is there anything about the drug that makes you choose oxycodone long-acting versus Opana long-acting, or is it simply that it didn't work on morphine, and you're going to go to the next drug. Or vice versa, is there anything else we can delve into about the basics? And I know the topic is difficult because a lot of it gets into basic science level questions.

For example, the CYP450 system. We have the story. We know what it does. Clinically we don't know exactly what

this means. So have you heard enough about the CYP450 story? Is that interesting to you? What more information would you like? Or do you feel that at this point the number of years it would take to produce a clinical study to show that some outcome is based on interacting and perhaps hundreds of thousands of patients to actually have some certain number of interactions.

NALINI VADIVELU, MBBS, MD, DNB: In practice we're doing (inaudible) mostly because we could use anything: IR, ER preparation Opana, injectable Opana. So people are usually going for the long term for Opana ER for chronic pain, especially the palliative care patients. That's when like they do not respond, probably because of all the receptors and everything, they don't respond to other kind of opioids. So then they go on to this Opana ER.

However, they're still worried that they may not have good outcomes down the line because they're not really sure. So then you're talking about talking to the patients and like making some kind of a contract and a goal-setting. So we're going to see like maybe three months and just going to have a pain talk, just only pain in like three months or six months and see are your goals being met. Functionally, you got to where you are. Is the pain better and things? And if not, then we're going to either stop it. Stop it not in just one day. We're going to wean it off, take you

completely off the opioids. And then we're going to see, give you nonopioid therapy. And then maybe we will start you back later on at a smaller dose and see if that helps. So since I guess we don't have that many outcome studies, this was the plan people are talking about to do.

CHRIS HERNDON, PharmD: Out of curiosity, does anyone in here write for the IR oxymorphone?

NALINI VADIVELU, MBBS, MD, DNB: We have it at Yale, injectable.

CHRIS HERNDON, PharmD: The injectable? How do you dose it?

NALINI VADIVELU, MBBS, MD, DNB: We're using it a lot for the acute pain in PACU in the recovery room. We give it like start at .5 injecting. When people come out in the recovery room, they are like writhing in pain, so if they do not get response with the usual things, which is like fentanyl or hydromorphone, then we start them oxymorphone .5 injectable, and then give them like doses up to usually 3 milligrams over like a period of 10 minutes. And if that didn't work, then we think that maybe they didn't respond to oxymorphone. That's what we're doing.

But the palliative care people, they are using it much more. And this is like acute immediate post-op. We're not using it on the floors. But we do use it a lot in the recovery room. And then the palliative people, they use it

and even much more than we do with the cancer patients. They're more opioid tolerant, and they use a lot more opioids and we feel safer after we do that.

CHRIS HERNDON, PharmD: Thank you. So just to make sure that I do my job correctly, there's one more thing that I ask you guys specifically about, and that's the data in the elderly population and the change in AUC. Is that concerning to anybody?

MATTHEW WIEMAN, MD: So the patients that we had that were over 65 actually they had an increase in their C-max a about 49 percent so they required a lower dose to achieve that.

MALE SPEAKER: Is that supposed to be in a negative way?

CHRIS HERNDON, PharmD: Just feedback, positive or negative.

M. CARY REID, MD, PHD: I think positive. I think the key thing up on the slide or maybe the other one was the reduced effect on psychomotor function. I've just finished a couple of weeks of inpatient medicine. Now the number one reason why old people come into the hospital is fall-related injuries. So I think that's a huge marketing plus.

MATTHEW WIEMAN, MD: So you'd like to see more data?

ROB GATLEY, MD: [Crosstalk] a study for

oxymorphone, following up the incidence of falls of patients on oxymorphone versus perhaps other opioids.

MATTHEW WIEMAN, MD: I would do it. I would do it.

GAVRIL W. PASTERNAK, MD, PHD: You have to be careful in the elderly, though. I don't think this is unique to oxymorphone, but the elderly especially, either morphine where you have a lot of a renal component to excretion, as people get older, I talk to my kidneys every night. Usually they talk back about 3 in the morning. [Laughter] And they don't work quite as well as they did. They're kind of closely related. And so I think that educationally that's a very important issue with regard to the elderly, to be able to cut back the dose.

I'm just curious what happens in terms of the spread on the half-lives. For example, what would be the half-life in the elderly versus someone younger. And the other question I would have, which I'm just kind of curious about, is I hear a lot of talk about the cytochrome P450s, that with the oxycodone that people have different abilities to metabolize, to demethylate. Codeine is that way. Do you have a tighter range of half-lives than perhaps oxycodone does? Would that be an advantage in terms of predictability of dose, not getting too high on something because of prolonged half-life? Is that something to consider?

MATTHEW WIEMAN, MD: I'm not sure if I'm getting

exactly what you're saying.

GAVRIL W. PASTERNAK, MD, PHD: One of the problems with methadone not is that the half-life of methadone is from 12 hours to 48 hours.

MALE SPEAKER: As you increase the dose.

MALE SPEAKER: Pardon?

MALE SPEAKER: As you increase the dose.

GAVRIL W. PASTERNAK, MD, PHD: Even within a single patient. And so you don't know before you start where your patient is. Some people will accumulate it at a much different rate than others will, and that's when it's a possibility of getting into trouble. So knowing what the half-life really is enables you to be much more specific in terms of your dosing with less concern about someone accumulating over a course of ten days as opposed to five half-lives, right? Well, five times two days is ten days, whereas most patients are going to be three days or four days. So I'm just wondering whether or not your variability might be less than something like oxycodone, where that might be perceived as an advantage.

MATTHEW WIEMAN, MD: No, I mean, I see the value in getting that information.

MALE SPEAKER: I'm sure you probably have it already.

MATTHEW WIEMAN, MD: Well, all the way out to say

certain populations, and you were talking about the elderly.

RONALD J. TALLARIDA, PHD: (inaudible) question posed earlier, I'm not a clinician, so why we're just looking at the mechanism of oxycodone and that of hydromorphone. I'd say no. Since it is the active metabolite, I prefer it because I'm assuming that all of the action of oxycodone is due to the metabolite. So in some sense your Opana has that appeal I think, and it sounds as though it should be a simpler molecule to deal with in terms of its adverse profile. I don't know if that's true or not. And of course it probably explains a lot of why it's so potent compared to the oxycodone.

GAVRIL W. PASTERNAK, MD, PHD: There is strong evidence there that it's pharmacological, it's not molecular. That points out differences between oxycodone and oxymorphone. And there is a group that really believes that the mechanism of action of oxycodone is actually different and that it's not working primarily through its demethylation. And if that were the case, you'd expect the cytochrome P450s to really have an impact, wouldn't you? So I think that answer's up in the air. I mean, for codeine, that's what we generally believe, and a lot of people also believe that the same thing goes with oxycodone, but I'm not so sure that everyone believes that in this room.

MATTHEW WIEMAN, MD: Rob, is there anything that we

have missed before we leave this section?

ROB GATLEY: I think we've covered most of the issues here. We talked about euphoria and cognition in terms of falls. Drug liking in terms of those things. That's a little more iffy. That one study that was done with the recreational drug abusers who took one intact pill of oxycodone CR versus one intact pill of Opana ER, there was no comparison done of what happens if you crush the tablet. And when Webster did publish his study something like that this year with oxycodone CR intact versus oxycodone CR crushed, and it had a huge impact on likability. So there are limitations to that study. And although the study implies that oxymorphone is less likable than oxycodone, we don't know what would have happened if they were crushed or if they're abused or misused in some way.

JOHN PEPPIN, DO: I think if you want to make a lot of money, you make a tablet that's a third hydrocodone, a third Xanax. You score it so you can just take what you want. I'll tell you, southeast Kentucky, boy, you'd make a fortune.

MARTIN D. CHEATLE, PhD: What's the tolerance profile on oxymorphone versus oxycodone?

CHRIS HERNDON, PharmD: When you say tolerance profile, what --?

MARTIN D. CHEATLE, PhD: Do you build up tolerance

faster in one or the other, or the same? Like I said methadone one of its advantages is that it's slower in terms of building up tolerance.

CHRIS HERNDON, PharmD: I don't think that the medical literature has that data. But Norm Harden from RIC in Chicago published a paper a couple of years ago looking at the necessity for dose titration with oxymorphone. And it appeared to kind of stabilize out where you didn't need to continue to go up on the dose.

MARTIN D. CHEATLE, PhD: So better than oxycodone then.

CHRIS HERNDON, PharmD: Well, but it wasn't compared to oxycodone.

MARTIN D. CHEATLE, PhD: That's really what the comparison should be.

HOWARD A. HEIT, MD, FACP, FASAM: It's only the loss of tolerance because that's important as far as safety. Is the loss of tolerance related to the half-life or the molecule?

MARTIN D. CHEATLE, PhD: I don't know.

HOWARD A. HEIT, MD, FACP, FASAM: What would you say if somebody said, "When would I lose?" and a clinician says, "I have a patient on X. They're going to stop it. How fast do you think they would lose the tolerance?" What would you advise? And if they took the same dose again they'd be

in bad trouble.

GAVRIL W. PASTERNAK, MD, PhD: I'd just be guessing. Basically when we titrate in the animal models, and patients I don't think are that far off, we can take away 90 percent of the drug on a daily basis and take them out without any overt signs of physical withdrawal. And then after five or six days, they're really basically almost the equivalent of naive in terms of essentially the most actions. So it's a fairly rapid reversal.

I don't know if there's a differential reversal with regards to analgesia versus some of the other side effects. But the concept of tolerance is a very interesting one. In the cancer population it's very common, if not the predominant one, that once you have pain under control, you can maintain your patient on a fixed dose of drug for long periods of time, and then in a place where we see a need to escalate dose after a few months, usually that's recurrence of disease.

MALE SPEAKER: And the point is, that's not tolerance, that's disease progression.

GAVRIL W. PASTERNAK, MD, PhD: That's disease progression. And so what happens is the patients are tolerant in the sense that they're taking doses of drugs that are far higher than you would give to a naive patient. But it appears that tolerance can develop steady state. And

so you develop the tolerance, and then if you keep the dose fixed, you keep the level of tolerance fixed. And if you can adjust them, you can get adequate pain relief for long periods of time. And so I wouldn't be surprised if oxymorphone does that, but I'm not so sure it would be unique with oxymorphone based on that study that you had.

MARTIN D. CHEATLE, PhD: What would be interesting is the advantage of methadone, besides it's cheap, is that you get the NMDA receptor, you get the mu receptor. The tolerance level, you can keep them on low doses for a long time. If for some reason oxymorphone was similar in that effect or had an advantage over other products, that would be a big selling point.

GAVRIL W. PASTERNAK, MD, PhD: Kathy Foley did a lot of work on this back in the '80s and the early '90s. And she published on some of these things, where she saw cancer patients who were maintained on these drugs for six months, 12 months, 18 months.

HOWARD A. HEIT, MD, FACP, FASAM: Didn't some of the original research by Vincent Dole and Marie Nyswander published in *JAMA* in the late '80s have to do with the blood levels, and the steady state blood levels were associated with not gaining tolerance and likability.

GAVRIL W. PASTERNAK, MD, PhD: I'd have to go back. I don't know. But of course the doses they were using were

very high methadone doses, so that the patients would be so tolerant that they wouldn't want to abuse the other drug. So I don't know. You might be right.

ROB GATLEY, MD: Thanks for that great discussion. We drew a lot more out than I think we were anticipating. So we've planned now a break. A little bit behind. So why don't we get together again at a quarter to 11? There's refreshments off in that room there.

[break]

[FILE 3]

MATTHEW WIEMAN, MD: Okay, I think we'll get started again. I'm going to introduce Howard to take the next section. We're going to run to about 12 o'clock here. So Howard's going to talk about the continuum of care, and what we're talking about essentially is the different formulations available of oxymorphone -- ER, IR, injection -- and the potential for developing additional formulations. And the key things we want to draw out is how you use the things, what patients, what situations, what disease states, and what future directions and issues should be undertaken in these areas. Howard.

Oxymorphone Continuum of Care

HOWARD S. SMITH, MD: I'm going to run through some

slides, but largely this section here is just to really get a lively discussion of all of your thoughts and opinions on the existing formulations and products, as well as where to go in the future.

The available formulations of oxymorphone include the oxymorphone extended-release, the immediate-release, and the injection. Other formulations which are potential might be an oral liquid, suppository, transdermal, fixed dose combinations that we touched a little bit about. So does anybody have anything to say about oral liquid?

This would be potentially especially useful in palliative medicine settings, in settings where patients are not able to swallow because of aspiration risks or because they have vocal cord problems, head and neck cancer. But in many settings where some clinicians use transdermals, because of some of these considerations, an oral liquid would be an oral liquid would be a nice thing to have. Anybody have any suggestions, thoughts, opinions?

MATTHEW S. WIEMAN, MD: Would anyone see in using an oral formulation of this, the idea of a continuum of care, does it matter to you?

JOHN PEPPIN, DO: No. In the hospice setting, well two things. Firstly, I really think the company could get a lot of mileage from just giving the product to hospice or just giving it at cost or whatever. Because most hospices,

they've got a margin like this. That's why they use so much morphine, and we have a lot of problems with that. First issue. But secondly, the liquid and a rectal suppository if, and I was going to see if your delivery system doesn't allow rectal delivery, because of course you can do that with a lot of things, you can put it rectally.

MATTHEW WIEMAN, MD: It hasn't been tested, but technically I know what you mean. We had the suppositories, no longer currently.

GAVRIL W. PASTERNAK, MD, PHD: Are there any people that use suppositories other than the French? [Laughter]

JOHN PEPPIN, DO: We do on hospice. When someone can't take orally. It's not exactly what they consider the optimal route. But the French seem to like it.

MARTIN D. CHEATLE, PhD: Do you have data on that? [Laughter] They always tell you to "Stick it." You're making an assumption that isn't positive.

JOHN PEPPIN, DO: Marty, there's only data in French rats.

[Laughs]

STEVEN P. COHEN, MD: Transdermal always makes me nervous in terms of abuse potential. So I don't know.

MALE SPEAKER: How so?

MATTHEW WIEMAN, MD: That's also some limitations, just to let you know, with this molecule with transdermal

formulations at that point.

GAVRIL W. PASTERNAK, MD, PHD: It is water soluble. It is too weak.

MATTHEW WIEMAN, MD: Yeah, there are some limitations to it. We want all ideas so that there's a potential for discussion.

GAVRIL W. PASTERNAK, MD, PhD: One thing that strikes me about pain is that at least in the cancer population, which is where my experience is, is that pain's not a constant. It goes up and down as the day goes by. And as the patient gets out of bed to go to the bathroom, that's when the pain is more intense. When the patient's resting in bed and at ease, they don't need as much. The transdermal approach is great for a baseline level, but it takes away the ability to titrate. So I'm not as keen on the transdermal approaches as I am with the others.

MATTHEW WIEMAN, MD: And right now the molecule in general is not really quite suited to it. But thank you.

JOHN PEPPIN, DO: What about intranasal?

GAVRIL W. PASTERNAK, MD, PhD: Butorphanol was a great drug. It had IV. Its blood levels following intranasal were identical to IV injections. For incident pain, it was wonderful. The drug itself was a partial mu agonist and had other issues, but when you're lying in bed and you have to go to the bathroom and you need something to work relatively

quickly, if this does work intranasally as a breakthrough pain type of medication, I think that would be kind of helpful. Whether or not it's going to be sufficiently commercially viable, I don't know.

MALE SPEAKER: Or approved.

MATTHEW WIEMAN, MD: And can I ask, as we think about this, let me just ask you from the top level, too, is in general what we're really kind of wondering is does this matter to you that you would have like you do with certain -- we'd be one of the only ones at the time -- that you have an IV, you have an IR, you have an ER, so you have is a continuum. You could go if it works, you don't have to stop. And in fact, we have a new formulation that's designed to be crush-resistant, so that's a different category. We can get into the discussion about what we could do with IR obviously or liquid has different technology barriers to making some of this. And IV tamper-resistant.

However, while were e talking about each of these, does it matter to you that you could prescribe, I f you're on oxycodone, do you try to use oxycodone for your breakthrough and why. And if that's the case, would you like to hear more about oxymorphone IR and would you be interested in kind of the injection as well, knowing what your patient has experienced from the beginning to end?

HOWARD A. HEIT, MD, FACP, FASAM: I think in the

clinical world, having hopefully a ratio of what you use as far as oral, IV, immediate-release of the same molecule, I think that's a major plus in the clinical world because again, because of different pharmacogenetics, and I'm certainly not an expert in that and we have the people around the table who are. Going away, the bottom line is the equianalgesic tables are a thing of the past. That's the bottom line.

MATTHEW WIEMAN, MD: That's good to hear, as well.

MARTIN D. CHEATLE, PhD: And also product users are people of habit. So if you have a product that goes across a variety of different forms, I need someone who has thrush, and I can't give them PO, and I can give them an oral liquid or something else, they tend to use the same product over and over and over again.

GAVRIL W. PASTERNAK, MD, PHD: That you know works, and you know the side effects for that particular molecule in that particular patient are tolerable.

MARTIN D. CHEATLE, PhD: And it has to do with time, also. If I know that, I can just use one versus the other, depending on the clinical situation. Probably use it more often.

GAVRIL W. PASTERNAK, MD, PHD: I think it's much more likely, for example, in a post-op setting or someone who's really sick is getting an IV infusion to switch them

to the same oral medication that they're getting IV. And I think that the immediate-release back in the old days with MS Contin, that's how we used to titrate the dose. We used to give the MS Contin and then you used to give them immediate-release morphine. And then the next day you would incorporate the immediate-release morphine into the MS Contin. Having the same compound as a rescue dose, for example, as you're titrating up your ER I think would be helpful, as well.

STEVEN P. COHEN, MD: I think that's true. So morphine and hydromorphone are available same way, right? You have IV, but neither of those in the operating room: Fentanyl is more commonly used, and in the outpatient setting, oxycodone, and either hydrocodone or oxycodone are more commonly used as sustained-release. So I mean, I definitely hear you. I don't think it affects practice as much as maybe it should or we would like to believe. So I think it's definitely a positive thing, but there are other products out there that do it. It doesn't seem to me to have made a huge difference. It's not like we're all using morphine because it's an IV.

GAVRIL W. PASTERNAK, MD, PhD: I think that depends on the population. In the cancer pain population, we have an awful lot of patients in the hospital that are not post-op, that have not gone and had surgery that are on morphine

infusions. And fentanyl obviously has advantages in terms of the on/off, where you just stop the infusion and then the drug goes away. So you may be right in many situations, but there are going to be populations where I think making that conversion.

Someone comes into our place in acute pain crisis, and you start them off on an intravenous PCA with a basal rate, and then all of a sudden they're starting to get better, and you want to get them home and you want to get them over to an oral regimen to manage them I think in that situation. Now, that may be a very small percentage, but I think there are situations where that could be helpful.

MATTHEW WIEMAN, MD: I think the whole story, actually there's limitations to it. And I think what you said was kind of key is should we. So the question I would ask is would it not, given some of the specifics of this molecule, so its lack of interaction with some of the other enzyme systems, some of the other potential values that we discussed at the very beginning, would it be valuable to start on a molecule that doesn't have those interactions, and then go down that line. That's where I saw some of the other value is not just using the exact same drug just because, but choosing a molecule like oxymorphone which might not interact.

And a lot of other competitors have different

formulations. Some of them have them all. But none of them have what we are going to have right now, which is an IV, an IR, potentially a liquid's an option, and then a TRF, our new formulation, which is designed to be crush-resistant. So of course that's a whole new discussion. And we can discuss that whenever you like. But having the entire suite of options available to you sounds like it's at least of interest. And maybe that's one of the things we might have to do to say why shouldn't we be doing it this way if there's an option to potentially better care. Any thoughts about that?

ROB GATLEY, MD: Another point, too, is having all these options available and availability is a big issue. As Steve brought up, there's a routine. You have morphine available. You have oxycodone available. But there's an inertia issue here. There might be some value having someone on IV oxymorphone because you're going to switch them to oral, but if it's not in the formulary, you're going to have to have a good reason to argue for it to be added to the formulary so you actually have the option. And that's an issue, the obstacles to availability.

HOWARD A. HEIT, MD, FACP, FASAM: Do you think part of it as far as switching or rotating through the same molecule as opposed to rotating to a different molecule where you don't know the variability and costs? I would

think it would be easier to switch to the same molecule in a different formulation than switching to a different molecule and then titrating up or down because you have to be very conservative when you make the switch.

ROB GATLEY, MD I think one of the issues that we need to try and find coming out of this is taking arguments like that as a leverage to get this on formulary so that it actually can be used.

GAVRIL W. PASTERNAK, MD, PHD: May I ask a very silly question? When Jack Fishman made all these things back in the 1960s, they were new and novel, and he made oxymorphone, oxycodone, naloxone and naltrexone. Not a bad job. But with regards to an intravenous formulation or an oral formulation, what kind of intellectual property protection do you have? What is to prevent someone from just getting the drug and selling the drug as a drug to a pharmacy, which them makes up their own? And most of your hospitals for intravenous might do that. I'm just curious from the industry perspective, how do you protect that and does it matter, or do you think it's enough of a lead-in that you don't care, that you'll make it up on the secondary oral from the IV? I'm just curious.

MATTHEW WIEMAN, MD: I'll look for legal help in the room because I don't have that. But I can tell you that it's definitely a consideration. This definitely the

discussion would lead to those details to say, first it's can we. Would it be good? Can we, should we, can we possibly afford it? And it's an extremely valid question, which is kind of like formulary. And in the end if we can't do it or if you're literally spending money, the company has to bring in revenue to be able to produce these drugs. So it's a valid question. I personally don't know the exact details about how the patent would be on those formulations themselves, but I can certainly find out.

JOHN PEPPIN, DO: It depends on how your patent's written.

MATTHEW WIEMAN, MD: Yeah, formulation versus --

MALE SPEAKER: (inaudible) the patent that's written covers IV and covers every delivery (inaudible)

GAVRIL W. PASTERNAK, MD, PHD: Well, I don't know. But composition of matter has to be in public domain. I mean, I worked on them when I was a graduate student.

NEIL H. SHUSTERMAN, MD FACP: It's been gone for decades. Composition of matter has been gone for decades.

GAVRIL W. PASTERNAK, MD, PHD: Absolutely. So when you have an extended-release, your patent is on the release mechanisms or on the pill itself or how you make it. But for oral and for IV, all you do is you take the molecule and dissolve it. So the actual cost of designing it is pretty minimal, but on the other hand, all someone has to do is

sell the powder.

MATTHEW WIEMAN, MD: I won't go into it too much, but we do currently have some patents around producing the actual raw form of the during however with the specific criteria and manufacturing strength. So again, I don't know the exact how that translates, but it's a great question. I can't answer that. You bring up a great point, though: Can we do it? Is it going to make anything for the company so we can move on?

But one of the questions I had overriding as well, which goes back to what I think a lot of us agree to, if you have IV in the hospital, are you more likely to become comfortable and inherently better at using that medication so that later down the line you may have more of a chance of having this in your armamentarium and actually choosing it with comfort?

MALE SPEAKER: Yes.

MATTHEW WIEMAN, MD: And how much of an impact is that, and would that potentially overcome some of the potential barriers with financial impact?

CHRIS HERNDON, PHARMD: I think it would be a much easier sell at P&T, but you'd have to be competitive with the other drugs. I mean, even with the shortages that we're having with getting a hold of some of that stuff right now, it would be a much easier sell if it was this, which may be

better in certain circumstances and the cost is somewhat comparable. But I think a lot of it boils down to that. But if you could show like in same-day surgery or in the PACU that throughput is better because you're not having to tinker with dose finding and how much oral are they going to need to get them out the door. I think a lot of that comes down to the financial. I mean, I know patient care is important, but unfortunately that's not always the driver for decisions.

MATTHEW WIEMAN, MD: What Rob said ties into that, and what you had said, which is could some of the messages around safety and some of the other reasons, the story combined, all of a sudden the minor issues combined turn into a story that would make it attractive to have it available. And of course we'd have to make it somewhat financially available.

GAVRIL W. PASTERNAK, MD, PHD: Well, basically I think that this is a molecule that most people haven't had a lot of experience with at this point. So the first question a physician would ask I think is "What kind of patients and what kind of pain does is drug effective for?" And there anything that you can do to expand their exposure to the use of the drug I think would be advantageous.

MARTIN D. CHEATLE, PhD: Yeah, why is it better than the alternatives? So cost is (inaudible).

MATTHEW WIEMAN, MD: And if you never use it, you're never going to start to figure that out, aside from of course studies, which you had just brought up. I guess I'd turn it over to you for a second. With your experience in IV, do you have any comments about how you've seen it? Does it have any differences that you find? You've made a couple of comments already.

NALINI VADIVELU, MBBS, MD, DNB: Yeah. It's great to have all three formulations for us on formulary, and it's definitely like the go-to rescue drug. So when a thing works, that's when definitely it has a strong place for that. However, I would say like we have like 50 operating rooms and almost 200 cases a day. And if it can be used for something like fentanyl, which is like used pretty much in every case. The reason is and especially this is what all the anesthesiologists always talk about is that they don't want to use this. They will read about this on/off, like they come out of the other anesthesia with the fentanyl. And another thing is there have been a couple of studies or something they keep quoting about like there was an increase in the use of naloxone in patients who had oxymorphone intra-op, postoperatively. And they don't even want to go there or even try it. They kind of are concerned about that.

MATTHEW WIEMAN, MD: That's an interesting point because the data that that comes from to my understanding is

based on fixed dose, very kind of old style studies in which they gave them what we found out later, or the folks that were here at that time, were very high doses of oxymorphone. So they'd come out and get 20 and 40 milligram pills, and we would see results where a lot of them had side effects.

NALINI VADIVELU, MBBS, MD, DNB: These things have to be clarified, you know? And I guess the doctors have to understand that info. That may be more marketing. I don't know.

MATTHEW WIEMAN, MD: So perhaps some data with the new study models.

NALINI VADIVELU, MBBS, MD, DNB: Yeah. And then it's like Martin just said how the doctors are so -- no familiarity. If they are familiar with something, and you already know what to expect, what are the possible side effects, and you've done this before, you've treated those side effects. Things are moving so fast and you just don't want to get into some waters it's too hard for you to handle. I think just the fear. It may not be true, but --

MATTHEW WIEMAN, MD: Because the other thing you mentioned is what was the -- that makes sense. You come in, fentanyl's great. It's on, it's off. Surgery is over. Quick, stop it. We go out. We didn't give him much.

NALINI VADIVELU, MBBS, MD, DNB: And that will be competitor. Even in the PACU you use methadone. And then

it's also like (inaudible) significant long half-life.

MALE SPEAKER: (inaudible)

NALINI VADIVELU, MBBS, MD, DNB: I know, I know. But for a really short time, for just that recovery room, for half an hour.

MATTHEW WIEMAN, MD: Well, what's interesting is that again some of that may be a misunderstanding because the half-life with the IV is quite short.

NALINI VADIVELU, MBBS, MD, DNB: But I'm saying what people are using. I'm not even saying about the science. But all these things have to be available to the doctors more.

GAVRIL W. PASTERNAK, MD, PHD: Does this have a QT problem?

MATTHEW WIEMAN, MD: Excuse me?

GAVRIL W. PASTERNAK, MD, PHD: Does oxymorphone have a QT?

NALINI VADIVELU, MBBS, MD, DNB: You see, all these are big advantages which have to be --

MATTHEW WIEMAN, MD: Yeah, there's no QT flags that I'm aware of.

[Crosstalk]

STEVEN P. COHEN, MD: I had written like a very inflammatory thing to guidelines for methadone, in like a response their guidelines in *Annals of Internal Medicine*. I

was doing a review. And I saw that oxycodone, and they were like some isolated reports, not like methadone or TCAs or anything like this, with QT. So I would guess the drugs are closely related. Like I said, it's neither here nor there.

NEIL H. SHUSTERMAN, MD FACP: We measured it in the clinic. We obtained EKGs, and thorough QT study was not required at the time of approval for this drug.

NALINI VADIVELU, MBBS, MD, DNB: I don't know how to get, maybe more studies or maybe more physician education.

MATTHEW WIEMAN, MD: All right.

NALINI VADIVELU, MBBS, MD, DNB: Yeah, we're lacking in that. I just brought this one here. Of course I'm not supposed to give it, I mean to you like that from me. But I can just say what we use. Like he was just asking what is the interconversion we use. Maybe that's not what you recommend. But normally for 1 milligram of IV of oxymorphone we convert it to 10 of the pill, the IR.

MATTHEW WIEMAN, MD: That is what is on the PI now.

NALINI VADIVELU, MBBS, MD, DNB: Yeah. And then usually for breakthrough we give PO like sometimes even up to 20. And we expect to see a result in like three to six hours.

MATTHEW WIEMAN, MD: Now, you had said kind of last resort, as the end of the line.

NALINI VADIVELU, MBBS, MD, DNB: Yeah, yeah.

MATTHEW WIEMAN, MD: Do you see that is there any change in that over time? Have you seen people think this may be better off at an earlier stage?

NALINI VADIVELU, MBBS, MD, DNB: Yes. The fact that it is on the formulary has definitely changed over like the last three, four years. When it first came, and even now it's only restricted for the acute pain service or for the palliative service. It's not available for every physician in the hospital now. But even within these two services which are allowed to use it, we've started using them a little bit more just because it's available.

HOWARD S. SMITH, MD: Have you noticed that there's more oral use, as well?

NALINI VADIVELU, MBBS, MD, DNB: Oral use?

HOWARD S. SMITH, MD: As follow-up.

NALINI VADIVELU, MBBS, MD, DNB: Oxycodone is very close. They first would like to try oxycodone and like Dr. Pasternak says, most of the time it works. But then sometimes we use it, once in a while. In palliative care it's a totally different situation, using it like much, much more, IV Opana.

HOWARD S. SMITH, MD: Opana.

NALINI VADIVELU, MBBS, MD, DNB: Yeah, IV and IR. And then discharging them with ER.

HOWARD S. SMITH, MD: So it seemingly it may have made a difference.

NALINI VADIVELU, MBBS, MD, DNB: Yeah, there is a difference, no doubt. Because it's available.

ROB GATLEY, MD: What are you saying, Howard, that if someone has used IV oxymorphone for whatever reason, are they more likely to be followed up with PO oxymorphone?

HOWARD S. SMITH, MD: Yes.

NALINI VADIVELU, MBBS, MD, DNB: It will happen, I can tell you with the palliative. So far at Yale I can expect that. It happens. We haven't done a study to see how many percentage of people, but we can see that it's happening. But not so much in the acute postoperative pain. They tend to go onto oxycodone PO and then get discharged like that. The surgeons, too, are not familiar. So you have to get to talk to the surgeons, too.

MALE SPEAKER: Why does critical care hospice use oxymorphone? That's unusual with the hospices I know.

NALINI VADIVELU, MBBS, MD, DNB: They use it because they think that the patients are taking such high doses of opioids. You should see some of our patients take extraordinarily high doses of opioids, so they feel that it'll be safe for them. Nothing is going to happen. They could tolerate it.

M. CARY REID, MD, PHD: That's in the inpatient

setting. So we wouldn't see that in a home hospice or out-of-hospital setting. The cost would be prohibitive I think.

ROB GATLEY, MD: As far as familiarity, I know that in veterinary medicine, oxymorphone IV is used quite extensively, often in preference to morphine. We don't really know why. We haven't looked in the literature to see how that developed. But it's not a rescue medication in veterinary medicine. It's a first-line choice.

GAVRIL W. PASTERNAK, MD, PHD: Morphine in the veterinary population is a tough drug to use. You give it to the mice, they run around the cage. You give it to the rats, they lie down. You give it to the dogs, they vomit. You give it to the cats, God knows what happens, the proverbial cat reaction.

MALE SPEAKER: Horses run faster.

MALE SPEAKER: I'm sorry?

MALE SPEAKER: Horses, they run faster.

GAVRIL W. PASTERNAK, MD, PHD: Well, actually I think they're giving them other things. So I don't know whether oxymorphone has that same species variability that morphine does. But morphine really buries them. Well, what was fascinating was when my little puppies were ill, and I was talking to some people at the Animal Medical Center, which is just down the road from us. And my dog had a cardiologist. He had an oncologic surgeon. He had an

anesthesiologist. He had an internist because he had a little congestive failure. When they went to the ICU they didn't know whether to admit him to the cardiac ICU or the pulmonary ICU.

MALE SPEAKER: Better care than many humans.

GAVRIL W. PASTERNAK, MD, PHD: No question. But I was talking to the anesthesiologists, and they say that certain species of dogs they use different opiates in because they think they work better. So I'm just wondering whether some of that might be playing a role in the choice of oxymorphone as opposed to morphine.

ROB GATLEY, MD: Looking at what little I have of the literature, it's possible it's species-specific, and there's really strong reasons for doing it, or it might be just tradition. It's been around for a very long time, and veterinarians and surgeons used to use it. And like evolution diverged. The vets still use it; human surgeons don't. Some of that might be research. When Opana ER came out, it was studied in indications for chronic pain. It was studied in low back pain. It was studied in osteoarthritis. It really wasn't studied much in situations of someone's in an acute situation, surgical, then going to an oral from surgery from an acute situation. So there isn't really a body of literature on that. To show that might be helpful.

GAVRIL W. PASTERNAK, MD, PHD: Yeah, but

oxymorphone has an extraordinary body of literature in the veterinary world. I mean, all the initial evaluations of these compounds back in the '60s, '70s, '80s were all done on rodents and done on dogs. So the veterinary population doesn't have to work on the FDA studies. They've got all the original studies exploring the molecule itself.

MARTIN D. CHEATLE, PhD: They're more discerning than surgeons.

GAVRIL W. PASTERNAK, MD, PHD: Well, we heard this morning that they spent five times the amount of time learning about pain killers.

MARTIN D. CHEATLE, PhD: So I think the business issue, you have to first demonstrate that it's a better molecule. Otherwise, why should I use one versus the other, and if you can demonstrate that. And second is I think people are more comfortable. I did a consult at a 600-bed regional hospital. All the inpatient is handled by hospitalists, who have very little training in any of this. And their biggest questions and concerns are, "I have someone on a PCA with this, and how do I get him out of the hospital." Now they're incentivized to get people out, so they're really motivated to do it.

And all the consults are about how do I convert this to this and what can I do? We did an audit, and there are like four or five Narcan cases per month because they

were just so unfamiliar with the drugs, they were just flipping from one to the other and not knowing the conversion.

MATTHEW WIEMAN, MD: So I'm hearing safety and money right there.

MALE SPEAKER: But first you have to say it's a better molecule. Then you have to say that maybe it's a safer sort of policy to stay within the same molecule base when you're converting. And hospitals, again, it's patient satisfaction they get reimbursed on, but also length of stay is important. So if you can get someone out of the hospital faster, that's a selling point. And if it's easier to convert from here to here, I think that's a good point.

KAREN F. MARLOWE, PharmD: (inaudible) people coming back.

MALE SPEAKER: Right, right.

CHRIS HERNDON, PHARMD: AND that's I think the key.

KAREN F. MARLOWE, PharmD: And if therefore discharging them on something that they've been doing well in-house on. Because what I see my residents doing is they switch them to the discharge med on the day of discharge, which is something that no matter how much I teach, they still do it. And so they make the conversion, write the discharge scripts and the papers and send them out the door. And within 48 hours they're back in the ER with uncontrolled

pain or some adverse effect, and we have to readmit them, which is now a huge event that we're going to be penalized for.

And so if we could discharge them on the medication they've been theoretically doing well on and on the PCA or IV, and have them do well at home, now even if we have to make some dosage adjustment at home or send them home with some kind of breakthrough that is a consistent medication, that would be wonderful.

MARTIN D. CHEATLE, PhD: That's our continuum.

KAREN F. MARLOWE, PharmD: That's the continuum.

MARTIN D. CHEATLE, PhD: What I see all the time is they'll go from like PCA with high dosing of morphine or whatever. Then they'll switch them to something else, and then they'll discharge them with Percocet. So they're kind of going down this way, and then the patient goes into the ED as opposed to going from injectable to extended-release plus breakthrough and getting him out. They aren't going to come back. And so it is an education process. But it is, it's familiarity. I know what to expect from this.

GAVRIL W. PASTERNAK, MD, PHD: There's also the lack of incomplete cross-tolerance when I make that conversion. When you're converting from morphine to methadone, that's the classic one. But those tables that Ray Hood developed back in the '50s and '60s really were on the

basis of the naive patient conversions. And those ratios we all know do not hold up when you're dealing with a tolerant patient. I think from the safety perspective, that's also a point to make.

MARTIN D. CHEATLE, PhD: This one case review is amazing. This guy came in, I forget what his pain problem was. But they put him on morphine. They had him on a PCA. Then they went to oral morphine. Then they added a fentanyl patch. Then they added a high dose of gabapentin. And this guy had three different cases of Narcan injections because of all this. And they just didn't know what to do with him. They didn't know how to control the pain. And I think if you just make it really simple and very, we go from IV, we go to this, we go to extended-release, then we get you out of the hospital. It's much easier.

JOHN PEPPIN, DO: It's interesting. We did a study in Lexington on the use of Narcan. It was over the space of a year. And I think the resident who did it had almost 100 patients who had received Narcan. And there's actually a protocol in our hospital that's been there for over a decade. Nobody uses it. The protocol says if the patient's doing this, then consider Narcan. So what we looked at was Narcan was used. Was it used appropriately based on that protocol. None of them, none of them we're appropriate. I mean, it was really shocking. It was very shocking.

HOWARD A. HEIT, MD, FACP, FASAM: I think you have to sell the idea of an oral PCA. When you're going from an IV, you go to oral patient-controlled analgesia. I think that's just sort of like a catchy way to do it.

MALE SPEAKER: Self-titrateable?

MALE SPEAKER: Mm-hm.

NALINI VADIVELU, MBBS, MD, DNB: I have a suggestion.

HOWARD A. HEIT, MD, FACP, FASAM: The point is that it is immediate-release.

NALINI VADIVELU, MBBS, MD, DNB: I think that if like Endo had a booth say like in the ASA, American Society of Anesthesiology or the postgraduate assembly, if you really get the anesthesiologists to learn (inaudible) where they could learn and start using it. Because we have like 30 to 40 million operations a year in USA. And so then once they start using it, the surgeons will get more familiar and they'll start discharging their patients, because they're the ones who write the scripts for discharge. They might discharge them on oxymorphone.

MATTHEW WIEMAN, MD: That was the thought. That may be a possibility. And one thing you mentioned at the beginning, too, one of the other ideas was that again fentanyl, it's quick, it's on, it's off. You need to get them in, you need to get them in recovery and then out.

But lots of cases that I would do would be this person's not going home, or it's going to be an extended stay, or they're going to the ICU. If it's a big case, or it's far enough in, I'm okay to give 5 mgs of morphine now. I've been whisking fentanyl along, it's going to be a little longer. So in my eyes, I guess I would ask, is there any reason in those longer cases or patients you know are staying in or are going to be in a controlled setting, why wouldn't you be able to use oxymorphone, aside from right now formulary issues. Is there any barrier to that in your eyes? Any place for a drug like that?

NALINI VADIVELU, MBBS, MD, DNB: For us it's just restricted for the pain service. It's not for the regular anesthesia or just for intraoperative use. It's not really for intraoperative use.

MATTHEW WIEMAN, MD: So maybe data on this stuff?

CHRIS HERNDON, PHARMD: Can you replicate the studies you did comparing like a CR oxycodone and extended-release Opana to your IV formulations? Because a lot of our people that come in, they want their hydromorphone or their fentanyl. I mean, is there data on likability of IV oxymorphone compared to some of the others?

MATTHEW WIEMAN, MD: That's the only one we have out there was the two of those, euphoria and the psychomotor testing. But these are the examples that I needed. This kind

of data may be helpful to again exposing, showing the data, having it available so folks get used to it.

ROB GATLEY, MD: That is important. There is a great lack of data on the use of IV oxymorphone. And the cases you talked about are complicated people. Palliative patients, they've got comorbidities. They've got lots of medications. And I think, Cary, in geriatrics, that's a very common situation. But I don't see anything having been published. You've got these complicated patients that are getting IV oxymorphone, how do they do. And can that be compared to patients who are complicated who are put on morphine? There really should be something in the literature about these are the sites that are using it for this reason, and these are outcomes. That kind of data would really help establish to clinicians whether it's valuable to pursue using IV.

MATTHEW WIEMAN, MD: And the thing about that is that you're naturally now doing studies. You're now exposing centers to being able to use the drug. So it's a study, but yet at least now a certain number, depending how we do it, will have had access to it. In a certain number of hospitals and some of these academic centers, it will be an option.

STEVEN P. COHEN, MD: Even the less euphoria is really a double-edged sword. You know that. There's no reason in the world that oxycodone should be so much more

popular than MS Contin. It should be the opposite, right? Because morphine is older. Everyone knows morphine. And it's cheaper. I mean, the fact is that these patients, at least the ones with chronic pain, they're all suffering psychologically. They have social issues. They're depressed. They can't sleep. And if you give people a drug and they feel better, even if it's because they feel euphoric, they still say, "This drug works. This one doesn't work. I feel better when I take this than morphine."

So we all say it's great to have less euphoria, that this is good. But in reality when it's practice and people come in, they prefer the drug that makes them feel psychologically better. Because we all know that pain is not just nociception. Pain there's a cognitive component in pain. And so I think it's a good selling point to doctors, but in reality --

MATTHEW WIEMAN, MD: Yeah, sometimes you want to create euphoria in someone who's in horrible pain. It would help.

MALE SPEAKER: Yeah, these people don't have great lives.

MATTHEW WIEMAN, MD: Now for something like that, here's an angle on that. Then we talk about euphoria, cognition, psychomotor like in one group, although they're three separate topics. So one of the thoughts that I had was

potentially, and we've all been discussing it, is would the outcome for this be more important to talk about psychomotor outcomes, falling, staying on line, as opposed to "How high am I today?" or "Can I still drive the car?"

HOWARD A. HEIT, MD, FACP, FASAM: You don't want to go there as a company using the word "euphoria". You want to go out doing studies as far as likability.

MATTHEW WIEMAN, MD: Likability, yeah.

HOWARD A. HEIT, MD, FACP, FASAM: But you don't want to go promote in any way, get out in any way, shape or form euphoria associated with your product.

ROB GATLEY, MD: I think if we're talking about intranasal or inhaled oxymorphone, which is one of the ideas that was just kicked around earlier, that would be an issue because that's the butorphanol story, the Stadol. It's really a molecule with low likability, butorphanol. But when it was put in that intranasal administration kit, yeah. Because of the very rapid onset of effect, it had effectively a lot of likability.

GAVRIL W. PASTERNAK, MD, PHD: It was only done intranasally because it was so basically inactive orally. They couldn't make a pill that had enough bioavailability.

ROB GATLEY, MD: I'd assume with oxymorphone you wouldn't have the 10 percent bioavailability. You'd have 100 percent, just like if it was IV, if you went to intranasal.

That would be a consideration.

MATTHEW WIEMAN, MD: Okay. Is there any specific data now that we're talking about? We clearly would like more data. You're saying there's interest.

GAVRIL W. PASTERNAK, MD, PHD: I think that the conversion from IV to immediate-release, immediate-release to continued-release, and preferably at two different levels of tolerance I think that would be very helpful. And that would be very nice in terms of selling: the ease of converting the people, as we saw before. And to show that you can use those conversions at different levels of tolerance with the patient I think would be important, particularly because as you get more tolerance, the incomplete cross-tolerance issue, switching from drug A to drug B, becomes much more of a problem.

RONALD J. TALLARIDA, PHD: (inaudible) [Any info on fixed dose?]

MATTHEW WIEMAN, MD: Not right now. No, we don't.

KAREN F. MARLOWE, PharmD: I don't know if it's possible given the chemistry of the agent. The liquid morphine we know is primarily the elixir. But if someone could take the liquid and give it more of an extended-release property so that our cancer patients could still get the benefit.

So many of their caregivers have to be able to get

up through the night and have to be able to go Q-two-hours with that liquid formulation. If somebody could take that liquid and be able to, like some of the transplant people have been able to do and give it a liposomal form or a microemulsion so that it had extended-release properties, so that primarily the palliative care folks could get the benefits in an extended-release, I know that that has a lot of implications for the abuse potentials of a liquid formulation. But I don't know that it's any more than just having a liquid formulation out there. But as far as the benefits to that population, I think that would be huge for them.

MATTHEW WIEMAN, MD: I'll turn that over to Dr. Pasternak.

GAVRIL W. PASTERNAK, MD, PhD: Well, first of all if it's liquid in solution, unless you're going to complex it with something, which I wouldn't. Then it becomes a new chemical entity. But when we talk about an oral liquid, I don't know that it really has to be in solution. It would have to be able to get down an NG tube. It has to get through a gastrostomy tube. And there people make these slow release formulations with these little pellets inside. If you could make those pellets sufficiently small, you could presumably still have them in an emulsion where you could actually put them down the tubes and get exactly what you

would like, which would be a slow release.

MALE SPEAKER: I've taken the capsule of Avinza and they're microbeads.

HOWARD A. HEIT, MD, FACP, FASAM: Right, taking a microbead and just putting microbeads into that.

ROB GATLEY, MD: I wonder is that even necessary though? Because oxymorphone does have a fairly long half-life. And if you look at the immediate-release, I mean, there's nothing to delay its absorption. Just it's poorly, slowly absorbed, so it ends up with a seven-hour half-life.

GAVRIL W. PASTERNAK, MD, PhD: I don't know the data for oxymorphone per se, but one of the most striking things about opiates has been the lack of correlation between plasma half-lives and analgesic duration. And I think the best example of that would be methadone, where the presumed half-life is, quote/unquote, 24 hours, and yet we have to give it every six to eight hours for pain control. So I mean, if you could show that, then that would be fine. But my guess would be, based on the other compounds I am familiar with, that the half-life is going to not be a very good predictor of the analgesic duration of action.

STEVEN P. COHEN, MD: But there are other long durations, like Kadian, possibly Avinza, I don't know, where you can actually crush it, stick it down an NG tube and have analgesia for 20 hours or 24 hours or something. So it's not

like it would be unique. Or methadone you could do the same thing to, right?

MATTHEW WIEMAN, MD: Yeah. I mean, the goal with that one would be as you were saying, to make the pellets small enough. Because right now they're small. But if someone is basically unconscious or really can't swallow or very demented or massive tumor, I think one of the next steps would be to create an extremely small version of these micropellets if possible. And of course this is cutting edge, and we're thinking about what we can do next. The other thought I had, too, is there some formulation change that can occur with stomach acid or enzymes that it gels in your stomach and then at that point. This is the very beginning of these thoughts, but there are potential ways to think about how you could make this a slow release formulation.

GAVRIL W. PASTERNAK, MD, PHD: You can go with that high tech stuff, but I think if you can get Ensure down a tube, then you can get many of these things that we have that we're talking about down a tube fairly easily, as well.

MATTHEW WIEMAN, MD: Okay. It makes a lot of sense. We need data. But the formulation itself seems like a good idea? You would potentially find reason for it in your practice?

GAVRIL W. PASTERNAK, MD, PhD: When you say IV,

would that also include subcutaneous pumps?

MATTHEW WIEMAN, MD: That would open up the door to all of that. The idea is to get people used to it and find out the best patient population. And then from there any kind of unique delivery method. I don't see why we couldn't use it like morphine, all other things aside, in many, many cases.

GAVRIL W. PASTERNAK, MD, PhD: But the nice thing is that the solubility I think of oxymorphone should be much greater than morphine.

MATTHEW WIEMAN, MD: Yes.

GAVRIL W. PASTERNAK, MD, PhD: So for a pump, it might be more amenable to use.

MATTHEW WIEMAN, MD: That's a good point.

NALINI VADIVELU, MBBS, MD, DNB: I think they use it subcutaneous sometimes.

MATTHEW WIEMAN, MD: They do the IM subQ, yeah.

NALINI VADIVELU, MBBS, MD, DNB: Palliative care, yeah.

MATTHEW WIEMAN, MD: Great.

NALINI VADIVELU, MBBS, MD, DNB: But you know, like in our conferences, like they always have booths for say oxycodone booth and fentanyl booth, so that all the people are familiar with those kind of drugs. So if there was another small booth, explaining all these things like the

continuum of care, the different preparations, at least small practices might start getting interested, don't you think? What do you think, Steve? You are an anesthesiologist. You can say.

STEVEN P. COHEN, MD: The practice would be interested if you did which?

NALINI VADIVELU, MBBS, MD, DNB: If you had a little like exhibition, like inside these big conferences.

STEVEN P. COHEN, MD: You remember the ASA thing?

NALINI VADIVELU, MBBS, MD, DNB: Yeah, yeah.

STEVEN P. COHEN, MD: Okay, so I'm chair of ASRA this year. Look, I don't get any money. This is (inaudible) job. But I think that this is great that companies actually want to do this Because for instance, it's a great way to educate. And the conferences nowadays, I mean, ASA is just enormous. I mean, there's 20-something-thousand people. But the way that the conferences are designed now is there's like a mandatory hour and a half break where people go into those things and they see them. So it's not even that it's just like kind of parenthetically there. Basically they're designing to do this. And I think it also establishes loyalty. Everything is written over here. The company's name is on the program. It goes out with the sponsors. We'd like to thank this. So I think these are great things. I mean, look at all these companies that are really big.

I mean what separates one drug from the other? It's basically advertising. I mean, Lyrica is a nice drug. It's not any better than nortriptyline for anything. Nortriptyline is first-line treatment for all kinds of headache prophylactic, and all the guidelines, European, Canadian and ISP say that TCAs are first-line treatments, just like gabapentinoid drugs. But the only difference is its advertising.

And Pfizer does a lot of these things, also. They have outreach programs everywhere, Johns Hopkins. And I think that the company does a really good job because they don't specifically just have these out. They're educational programs, and you can go and you can speak. I went to Toronto and I spoke in Toronto. I didn't even know that it was being sponsored by Pfizer. My talk had nothing to do with Pfizer. And I showed up for dinner, and there was someone from Pfizer there.

I think that these really establish good publicity for companies. If I were trying to sell a specific product, and I think that this product is really good for that audience for something like ASRA because it's acute pain, it's chronic pain, and it's anesthesiology. All of them are together. These are the venues that I would advertise in. But again, I don't make these marketing decisions.

NALINI VADIVELU, MBBS, MD, DNB: It will be cheaper

for you. It will be cheaper to just go to these big conferences versus going to each and every hospital in the whole country, right? I mean, to start with at least.

ROB GATLEY, MD: [Are we getting the cart before the horse?] I'd like to start with (inaudible) because the advertising has to be based on data. And we're at the point now saying, "Well, we don't really have data about why it is useful to have IV." Are there case studies? Are there some small clinical trials? Or Pat actually from pain management nursing, a lot of these choices about formulation, what formulation is suitable for this patient fall across nursing. Just some data on clinical experience with these. That's the kind of thing that has to be established first, and then there's something to present at the booth.

MATTHEW WIEMAN, MD: Yeah, and this is the kind of questions.

MALE SPEAKER: But right now we're trying to find the stuff as the basis of what's at the booth. We don't have the data yet.

MATTHEW WIEMAN, MD: And this is the kind of questions we're asking from you folks. Is it interesting enough for us? Because obviously that's what it is. We're going to have to go get studies, create the data. Then have a presence scientifically, purely, because it's not labeled or anything like that. It's going to be based on research.

Then go to symposiums, research kind of seminars. And then eventually of course you could go commercial if it ends up going that way. But at least have a scientific presence, is that what you're saying, at some of these meetings?

NALINI VADIVELU, MBBS, MD, DNB: I mean, even with just what you have. You have all this stuff. Do you agree?

STEVEN P. COHEN, MD: You're absolutely right. I mean, look at, they come out with another muscle relaxant. There are 40 of them available. And you go and they advertise this thing. And it's the same thing for everything. A massage table. Have you ever been to these things?

MATTHEW WIEMAN, MD: Yeah.

STEVEN P. COHEN, MD: Someone gives you free massages and they have coffee over there. And people go over there and they buy the massage tables. There's nothing. You have a drug. It works. It's approved.

NALINI VADIVELU, MBBS, MD, DNB: We have some data. We need a little more.

STEVEN P. COHEN, MD: I'm not sure what data you're looking for.

[Crosstalk]

MATTHEW WIEMAN, MD: Not necessarily head-to-head. Just data to say "We've been there. We've done that. We do have data to show that you can use it IV and there's good

results. So it's safe, and there's not a head-to-head outcome, but we can show you. We actually have used it. We've studied it. Here it is." It may not be mind-blowing, but it creates an opportunity to discuss and disseminate the literature.

HOWARD A. HEIT, MD, FACP, FASAM: Well, you're never going to have head-to-head data are you?

MATTHEW WIEMAN, MD: Sorry?

HOWARD A. HEIT, MD, FACP, FASAM: You're never going to have head-to-head like oxymorphone to A, B.

MATTHEW WIEMAN, MD: It's very unlikely.

MALE SPEAKER: I think impossible because no company's going to submit to it because they'd lose the race.

NALINI VADIVELU, MBBS, MD, DNB: It's FDA-approved.

ROB GATLEY, MD: But there's other sources of data. There might not be randomized clinical trials, but experience and case studies. I think like Pat you just say something about pain management nursing because I think that's an area that the availability of formulations like this are important, as Karen was mentioning, there's a nursing issue, that it would be valuable to have an oral liquid that lasted a longtime so there would be fewer doses. A lot of times the quality of pain management has to do with administration of it. It's not going to work if the

patient's not getting it.

HOWARD A. HEIT, MD, FACP, FASAM: But then you're going to best clinical practices, which is fine, especially in pain management. There's so little hard data that the next best thing is best clinical practices, and that's what you're saying.

PATRICIA BRUCKENTHAL, PhD, ANP-C: But you have the practical applications. You presented that in the last slide deck. There are probably three points. You said earlier, your patients remember three points. I remember three points. But there are still three points from that last slide deck that I remembered about the older adult, the bioavailability, and the psychomotor. And that interested me as a nurse to have that information. You could still go out to these venues and present case studies or what's unique or why should I prescribe this drug if it was available. That's the sticking point again, and we brought that up from the beginning. It's difficult to get access to that particular drug.

ROB GATLEY, MD: And does that prove to be an issue. If you've got someone on a drug that's a tablet and they're not able to swallow it and you have to make a conversion. Is that really of value to know that there's another product, same molecule.

PATRICIA BRUCKENTHAL, PhD, ANP-C: I think it's a

big value, and that discussion came out: the continuum of care and not having to do the math and convert. I know you have to do the math to convert, but from the same drug to the same drug is a lot easier than from this drug to a different drug.

GAVRIL W. PASTERNAK, MD, PHD: It's the Windows 8 approach. [Laughter] Same operating system, multiple devices. Same drug, multiple approaches. I think that would be valuable.

ROB GATLEY, MD: There's one more topic we wanted to get out of this that I think is important. And that's there's been the abuse of long-acting opioids, of OxyContin in particular, so Opana ER has been reformulated as a TRF. And in that little window of time, as Neil's going to talk about, between when oxycodone became tamper-resistant and when Opana ER became tamper-resistant, there was a huge migration of abusers from OxyContin to Opana ER. So now Opana is known as a drug of abuse. It's got a popularity it never had before. That's also likely to pull abusers towards other forms of oxymorphone, like IR, which at present doesn't have any tamper-resistant features. It's extremely easy to crush IR. So that's another consideration in this topic of formulations. If the ER is tamper-resistant, should the IR also be converted to tamper-resistant? Would that make a difference to your practice? Do you think that would

be an important issue?

MARTIN D. CHEATLE, PhD: It will be important for publicity. If you said all the products were tamper-resistant, you would probably get interest from a lot of physicians.

HOWARD A. HEIT, MD, FACP, FASAM: The majority or abuse of the immediate-release or the continued-release is just taking the whole pill. Second is then crushing it. Third is shooting it, and fourth is snorting it.

STEVEN P. COHEN, MD: Yeah, and it really only deters a small percentage of abuse. So the people who are going to sell it or divert it, because there's lower street value, are the people who are going to crush it. But the people who just take two or three pills, it doesn't stop that. But the other thing is, the typical thing that I do and just because it's cheaper and you don't have to go through all the authorization, which again is a big, huge pain, is if someone's a good candidate for opioids, they go on something where you don't need authorization, a cheap drug, morphine, fentanyl, where you don't have that those things. Or you can take the transdermal.

The formulation by itself is abuse-deterrent. but then if somebody starts to exhibit a lot of aberrant behaviors, and I'm curious, they just go off. There's on irrevocable right for somebody with chronic back pain or

abdominal pain to be on opioids. And this is the practice of the large majority of people. If somebody is on morphine, and then they're testing positive on urine tox screens, or they're losing prescriptions or there's a lot of things, they go off. And this is the same thing. No one is putting these people on an abuse-deterrent formulation because again it's just a big, huge headache. And I think a lot of primary care doctors are looking for a reason to get these people who are escalating doses, off.

MALE SPEAKER: And fentanyl's very abusable.

MALE SPEAKER: Right.

MALE SPEAKER: The street value is about a buck and (inaudible).

MALE SPEAKER: They cut heroin with fentanyl all the time.

MATTHEW WIEMAN, MD: I think that's a good point. And I think that's one of the comebacks to the honesty part of why the academic honesty and transparency are right up front, which is that clearly there can be no claims made about the TRF formulations of any kind at this point. There's preliminary data. You're going to see some right after lunch, as well, the publications come out for OxyContin new formulation.

I guess the idea is does it matter to you that it's one more step. So it's the analogy of walking down the

street, one door is open. The next door is closed. The next door is locked with an alarm system. The folks that want to get it may get it, but does it matter to you that there's potentially, and again we're going to have to wait for the ultimately results, some incremental benefit in what TRF may bring to the market?

ROB GATLEY, MD: I think it's formulation-specific, too. As Howard was mentioning, the most common form of abuse is just swallowing tablets whole, and with long-actings the next would be chewing them. In the Lynn Webster study where he compared intact OxyContin to crushed OxyContin, he also compared it to Oxy IR, to instant release. And when they were taken orally, there was a huge difference between the crushed and the intact OxyContin. but between crushed OxyContin and intact Oxy IR, there wasn't really any difference in likability. So if there was a tamper-resistant version of oxymorphone IR for people who just were going to chew it, it wouldn't really make any difference.

MATTHEW WIEMAN, MD: And I can see, it makes sense. If you have a serious problem with a patient it's not a solution. But could it be part of your practice? Again, with oxymorphone to me it comes to why not start with a drug that has a TRF formulation if it's available. So that's kind of where I'm coming from with that. I don't see it as a silver bullet.

STEVEN P. COHEN, MD: It's a great thing, but the thing is a lot of the drugs that have a TRF formulation are even more expensive or you require authorization or there's REMS. And that's why people start with morphine.

MATTHEW WIEMAN, MD: Sure.

STEVEN P. COHEN, MD: And I'm not saying if you're an addictionologist, but if you're a guy in private practice. We had this yesterday. Someone came in, and it was written abuse all over, and they were wanting opioids I'm not going to put them on opioids no matter what. It's just a road that I don't want to go down. So I think it's great, but I think that when you create a formulation like this and then you have to go through loopholes to get it, whatever it is, filling out forms or having a talk or having to fail this therapy and this therapy or this therapy, authorization, then it becomes a problem.

MARTIN D. CHEATLE, PhD: That's why hydrocodone is still the most abused drug because people just say, "I don't have to do anything."

STEVEN P. COHEN, MD: It's easy.

MARTIN D. CHEATLE, PhD: I can give you 60. Now we're going to do REMS. I don't have to do that. I can always give you Vicodin. I can just give you hydrocodone. And that's why it's abused by everybody. Addicts go to what's available, period. And if you can do anything to

mitigate the risk, there's probably an advantage from the publicity perspective. I'm not sure it will really change anything.

MATTHEW WIEMAN, MD: You guys will see some interesting data, too, in Neil's section where there are some thoughts by different groups and some data that shows that there perhaps are some fingerprints of abuse for different molecules. So there's different routes of choice of certain different molecules. And you'll see it in context. It's pretty interesting. Rob, did we hit the last?

ROB GATLEY: I think we've hit pretty much all the points now. We discussed the value of the different formulations. We had some background slides that were really very similar to what Chris covered in his presentation. And with the formulations, we wanted to talk about what kind of patients you would use them for, in what situations. I think we've hit that with where IR and IV would be useful, and to wish-list formulations like oral solution, where that might be used.

MATTHEW WIEMAN, MD: Some of the settings will be interesting, too, because we broke it down to something about, so the IV. I thought about this patient type or the setting. So there's a lot of combinations of potential there that we could look at. So, where are some places, and we've started that discussion, where it may be used, and we may

find some good places for it.

HOWARD A. HEIT, MD, FACP, FASAM / ROB GATLEY, MD: Can you go back to the slide that had the graph on it just for a second? You illustrated something about absorption and that whole fat solubility. Because you see the two peaks there with the IR. That's because patients were fed at four hours a fatty meal, and that's one of the odd things about the absorption of oxymorphone ER. If it's combined with fat or with alcohol, it's absorbed more rapidly from the gut.

HOWARD A. HEIT, MD, FACP, FASAM: Right. Wasn't there just a paper published about cognitive ability, about taking it two, three hours after or taking it on a fasting?

ROB GATLEY, MD: Yeah, I think it's Gustason[sp?]? Yeah.

HOWARD A. HEIT, MD, FACP, FASAM: Last week.

ROB GATLEY, MD: Right, it was a Swedish group. That was an IAS study. They did show that there was a very minimal effect of patients who were fed on cognition.

HOWARD A. HEIT, MD, FACP, FASAM: And taking it fasting as far as their cognitive ability, reaction time.

GAVRIL W. PASTERNAK, MD, PHD: How much of a change in the differences in absorption with alcohol?

MATTHEW WIEMAN, MD: It ranges from negative to 270 percent increase, depending on the dose of alcohol you get. The folks that reached that level were taking 240

milliliters of 40 percent alcohol, so they were doing a beaker full of straight vodka. And they were made to drink it all at once. So it was an interesting study.

MALE SPEAKER: And a cheeseburger.

MATTHEW WIEMAN, MD: Yeah. What they found, the important thing about that is that there was a big range in what happened. In the end it wasn't discovered why, and when you did out the numbers, the C-max went up and down. But the overall area under the curve didn't change, so that's why they were able to say this wasn't like a Palladone dose-dumping type issue. However, it's absolutely true that you have very variable and usually rate of increase of the drug in your plasma with alcohol.

GAVRIL W. PASTERNAK, MD, PHD: The Palladone was the fact that they matrix they used was alcohol soluble.

MATTHEW WIEMAN, MD: Exactly. That's why I was saying it's important to note, it's true, we had this interaction. To caveat it, we don't know why. You should never drink alcohol with it, and we proved that it wasn't a dose-dumping phenomenon based on the area under the curve.

GAVRIL W. PASTERNAK, MD, PHD: By the way, they knew that about Palladone long before the launch.

MATTHEW WIEMAN, MD: I was not aware of that.

MALE SPEAKER: But your pills are not soluble in alcohol at all?

MATTHEW WIEMAN, MD: They showed no release. There was no dose-dumping of the pill if it was placed in solution.

ROB GATLEY, MD: It didn't cause any breakdown of the matrix. The effect was the same as fat. The alcohol had the same effect as a fatty meal.

MALE SPEAKER: The newer matrix actually showed slower release.

MATTHEW WIEMAN, MD: Yes, it actually slows down. It's polyethylene oxide, so it's actually basically a type of a (inaudible).

GAVRIL W. PASTERNAK, MD, PHD: I'm just wondering whether or not this may have an impact on the abuse liability if you're going to increase your bioabsorption 200 percent in the presence of alcohol, that seems like a party.

MATTHEW WIEMAN, MD: It's certainly something that is not recommended to do. We have found it. We don't know why.

MALE SPEAKER: There are a lot of things we don't recommend.

MATTHEW WIEMAN, MD: No, it's an important fact. And that's out there. It has to be dealt with.

ROB GATLEY: I think we covered the topics there. So we've got lunch until 12:45 in the same room we had for breakfast.

[lunch]

[FILE 4]

MATTHEW WIEMAN, MD: So as Neil says, we're bringing us back together. Post-lunch here, a little bit more of a push. I think we've had a really good set of conversations. I think we've hit on a lot of topics, which is the nature of this right now.

MALE SPEAKER: Question. I'm sorry to interrupt.

MATTHEW WIEMAN, MD: No, no.

MALE SPEAKER: This is what the product is made out of, which I found fascinating. This is the matrix.

MATTHEW WIEMAN, MD: It is interesting. No, thank you.

[Background Conversation]

MATTHEW WIEMAN, MD: So thanks again. Welcome back from lunch. Just a little bit more time. Just to keep everybody energized here. I think you're going to really like this next section. A lot of really interesting data on some of the initial preliminary results. And again we have another distinguished guest here: the Vice President of Clinical Development and Medical Sciences and Senior Medical Advisor, Neil Shusterman.

Effect of Reformulation of Opana ER on Abuse of the Product: Early Experience from Surveillance Data through 3Q 2012

NEIL SHUSTERMAN: Thank you, Matt. So, as I mentioned earlier, I spent most of my career in clinical development, designing clinical trials, conducting clinical trials, analyzing the results, defending the results to the FDA. But recently I moved over to the dark side: drug safety. So what I see every day is the bad, the ugly, and the uglier: about 601 reports of adverse drug reactions from spontaneous reporting each year, and whatever we bring in from our clinical trials. So I have a very skewed view of the world now than I did before. I don't see any benefit. I only see bad.

But anyway, I bring that up as a segue to actually going off-script for a couple of minutes because Matt graced me with 15 extra minutes, and I was wondering how I was going to fill them. And this morning as part of the early part of the discussion, I was interested a lot in what John had to say. And one of the premises, or I should say one of the supporting facts that I heard in evidence was that both at the undergraduate and the graduate medical level, there's not enough education about not only opioids, but proper pain management. And a lot of information along those lines was shared with the group.

So that's actually a lead-in to, if that's sort of

the starting position, then how do we educate people? And I know you can take it at any part in the training cycle you want, starting from medical student to trainee to obviously people practicing in health care professions. So the FDA did put into effect earlier this year the Risk Evaluation and Mitigation Strategy for the Extended-release and Long-Acting opioid products, otherwise known as the ERLA REMS. And all companies are mandated to be part of it. So I did want to correct one misimpression this morning. Not a single taxpayer dollar is going to that REMS. It's coming from all of the member companies, of which there are about, depending on who's getting new drugs approved. I don't think Zogenix will be part of it right way based on the committee meeting that occurred. But it's about 20 companies.

So what I'm interested in sort of stimulating a discussion on is the FDA has reached the conclusion, and I don't think it's an unreasonable conclusion, that if education is the missing element, why wouldn't supplying education be not a cure for all of the problems that ail this area in terms of abuse, misuse, and diversion, but wouldn't it be the right direction. So I'm kind of interested in why that theme didn't seem to play.

Probably a lot of people here have read a number of articles in the *Annals of Internal Medicine* and *JAMA*, people putting up relatively negative views about the FDA's

efforts. And please keep in mind, the FDA is nothing else is a regulatory body that needs to function within the laws of the land. So I've read a lot of those articles. There's a lot of ideas about out there, "Why don't they do this? Why don't they do that?" If they don't have the regulatory authority within law to do something, they're not allowed. That's what the United States is all about in terms of our system of government.

So for example, some people said it should be mandatory. All physicians to get their DEA license renewed should go through some kind of educational process. But what they're failing to understand is that there is no regulation. The FDA cannot do that. Until Congress puts a law in place that says that and it's signed by the President, they can't do that. So there's sort of this people saying things in press and leading to this general impression that the REMS is either a set-up for failure, which it might be. It might not work. But it's sort of what they have under their control under the laws of the land.

So at least going back to the premise of education, I would like some comments and feedback about that. Because we're spending a fair amount of our good money and our own internal peoples' time trying to make this work because that's what the FDA has asked from us, and that's what we're committed to do. And I wish Linda Kalinski[sp?],

who is our educational guru, were here to participate in this discussion as well. So I'll throw it open to anybody who wants to just comment. There's no right or wrong answer. I'm just interested in sort of if education isn't the answer, or this isn't the way to go about it, what works these days? What should be tried? What makes sense? Anybody.

PATRICIA BRUCKENTHAL, PhD, ANP-C: I'm thinking one of the issues we grapple with is what's the education, what are going to educate people about. I think there's probably different levels of learners. One thing we know is education in and of itself doesn't change behavior. So this is a really complex problem, and I know from teaching on the undergraduate level, the gradual level and then out to practice there are certain concepts that I think should be taught at a certain level and then the student or the learner hasn't been exposed to something, some concept, and so it's not valuable to them.

So from a practical reason, teaching the pharmacology of opioids is an important thing for a student to know, like learning how to use an antihypertensive or learning how to use an antimicrobial agent. That's important. But some of these other things that we're talking about, the complexities may not be as meaningful to people until they're out in practice.

NEIL SHUSTERMAN: But all this education is geared

to practicing physicians. I think many people probably have read the FDA's blueprints. I think a lot of things in there are basic, sound approaches: which patients you select for opioids, how you monitor them once they're on the drugs, when you take them off of that. I think a lot of that is actually missing from physicians' and health care providers' repertoire of what they do rather than just writing a script saying, "Take this. This will help your pain."

GAVRIL W. PASTERNAK, MD, PHD: There's also an extraordinary amount of diversity of opinion as to what you should do for each one of those points.

NEIL SHUSTERMAN: Yes.

GAVRIL W. PASTERNAK, MD, PHD: And that to me is a major issue. Education is great, but what's the curriculum? Who decides what we should say? And the problem, as I mentioned earlier this morning, is that you tell people, and then they hit other people that have a difference of opinion. When we tell the students, they hear us. They got the floors. They have other doctors they follow, different opinion. And it's right back to where we started. So the question I guess I would have is what criteria, what are we going to teach them. Is there anything that really is sufficiently established that everybody would agree that this is important, or are you going to have controversy, in which case people are just going to walk away from us

saying, "I don't believe it, and I'll believe the other guy."

NEIL SHUSTERMAN: Well, as I said, I think the blueprint itself gets to be interpreted by the education providers. The content is not dictated by the companies. And then the actual delivery of it is independent of us and is audited by the FDA. So from the standpoint of an educational approach, it's probably as good as things are in the 21st century. But I'm kind of looking if there's other kind of ways in an adult learning situation that maybe the FDA could have been more creative in how they went about in terms of education. [Laughter]

MALE SPEAKER: Sorry. I just can't keep my mouth shut.

NEIL SHUSTERMAN: I was hoping you would say that.

JOHN PEPPIN, DO: Well, first of all the FDA spent a lot of taxpayer dollars in the FDA. They're not funding the REMS programs, but they spent millions of dollars with committee meetings, et cetera, et cetera. So I mean, just to verify that point. Secondly, they certainly could have done things like make it mandatory, if they were willing to work with other agencies. They could have worked with the DEA. They could have made this part of just your DEA license. I'm not saying they should have, but they could have done that.

NEIL SHUSTERMAN: Not without legislation. DEA

doesn't have that authority either. They need legislation.

JOHN PEPPIN, DO: That is not absolutely for sure. I mean, they may well have had the authority to do that, the DEA now. But okay, apart from that. Basically the way the REMS has been formulated really is just very similar to what we've been doing before. So if I'm a talking head at a meeting, and I do a lot of that, right? I'm a ham. I like standing up and talking to people. Do I really change behaviors? Do I really make an impact? Not much. And the data shows that with CME.

And talk about creative. I mean, it needs to be creative. It needs to be interactive. It needs to be something very unusual. They need to work with adult education and come up with programs that are going to make a difference. But that's another problem with REMS: There is no evaluation. So what are we going to do? We're going to look in three years or five years, and if people are still dying from opiates, then what?

NEIL SHUSTERMAN: Well, there's an evaluation of the individuals who take the education and the success of how many prescribers we've reached and things like that.

MALE SPEAKER: I think that's smoke screen.

NEIL SHUSTERMAN: So the FDA uses a lot of the same sources of data that the company uses. So although they may not explicitly state that, I think they're kind of looking

in the background there of what's happening. And they've gone on record at least with us as saying, "If this is not reducing the outcomes you're talking about -- deaths from overdoses, abuse rates, things like that -- then they need to move in an additional direction or a different direction."

MARTIN D. CHEATLE, PhD: I think the problem is the way that REMS is set up, it's the archaic way of teaching. They don't do it in the medical schools anymore. We just got a grant at Penn from the Pain Consortium from the NIH to develop one of these educational modules for nursing, pharmacy, this and that. But we actually got experts from the learning center about how we can do this differently. And I think they didn't do that.

I like case-driven ones. And what we're doing is setting up scenarios. So a patient comes in with this, and here's when it went really well on script, and here's when it went really poorly. And they just found by using the right expertise that they can really get the message across in sort of case-based good and bad scenarios. And I even suggested they get like a communications person in. I always thought that was just for football players, but actually we did a seminar with a couple of communications people. They are really bright about how you hit audiences, how you communicate your message, identifying what the audience is.

So I think it's just such an archaic kind of again talking-head, just these are the points. I'm not sure it's going to have much of an impact.

STEVEN P. COHEN, MD: So they have to say that, you know, you see this all the time, smoking can be hazardous to your health. Everyone knows this. There's no one in the world who picks up a cigarette now who doesn't know that smoking can be bad. It's the same thing with alcohol. So the government is mandated to do things like this. So the army, you put young 18-year-old guys and 18-year-old girls together in a stressful situation, there's alcohol.

There's going to be complaints of sexual harassment, and it happens at all the academies. So now everybody every single year has to sit through a video that you shouldn't rape someone. If someone says no, they mean no. But these things still are going to happen. And maybe you can get very, very, very low-hanging fruit from this. And like I say, the government does this stuff all the time. Like war is an inherently dangerous job, you know, to be a solider, and so they can have you go through weeks and weeks of training, cultural sensitivity. If you didn't drop it on the ground, don't pick up unexplored (inaudible) And maybe you can save a couple of people. But people are still always going to die. And opioids, again, there's an inherent risk to prescribing these.

So what ends up happening is you start to -- sorry for all these clichés -- basically you're kind of punching tickets. Like, this is what we have to do, and this is the least painful way to do it. And it's a reasonable thing to do because look at, people, doctors know, everyone knows that opioids have a risk. This is what you should do. Patients know when they're doing something right and doing something wrong. I think some people you can make it safer, but for 95 percent of the cases where a problem happens, I don't think it can be prevented by REMS. So people take kind of the easy road out.

I think the government has to require things like this, just like if you're advertising for a chairmanship at Mass General. It has to go into a magazine, even though if you're some guy off the street and you say, "Well, I'd like to be the Chairman of Surgery at Mass General," you have no chance. But it's something it's actually mandated to do. They have to. It's a government organization. Sorry, I went way off.

NEIL SHUSTERMAN: No, I appreciate all these comments because this is something that we literally live and breathe every day. And we have to. We have obviously no choice because we're a regulated industry. Anyway, that was fun. I appreciate that.

So what I'm going to do today is this is really

the first audience that we've actually presented some of our surveillance data, which we've been monitoring ever since Opana was approved. And several years ago, obviously, as oxycodone went through a reformulation, we figured, well, the next big abusable drug on the blog was going to be us. And we partnered with the German company, Grunenthal, using their technology, with is the INTAC technology, to reformulate Opana in a way that resisted crushing. Now, bear in mind that the original formulation of Opana had a gelling agent in it, so it already tended to resist solubilization and therefore intravenous abuse has in general been a low frequency form of abuse. And the reformulation also has that gelling property through polyethylene oxide, as I think Matt mentioned, and that also becomes a gel state when mixed with water. So that barrier remains the same.

However, as I'll show you, the old Opana was very, very easy to crush. Anybody in this room could easily do it by just taking their first and reducing it to a powder on a tabletop. And therein lay the problem as I'll get to because nasal insufflation, snorting was the major route of abuse with Opana. And we felt therefore we needed to come up with a technology that would make it harder. Does it fix all the world's problems with abuse? Obviously not. Anybody who is dedicated, and we know there's people out there, will continue to find ways to get around that. But for those who

wanted the quick and easy way, they're at a party, they wanted to snort it, you just can't do it that easily, as I'll show you in a couple of minutes. That was the theory going through our heads as we developed this formulation. So, I've gone through a lot of that formulation history, but then I'll also show you some data since it's been on the market.

Everybody's seen this slide. I don't see how any of these talks can start without showing the magnitude of the problem. And we felt that being responsible to what we knew to be our specific contribution to the problem was the right thing to do.

HOWARD A. HEIT, MD, FACP, FASAM: It's interesting that the lines are always parallel to each other, directly related to the sales are the percentages, that the deaths go up in the same rate.

NEIL SHUSTERMAN: Treatment and sales.

MALE SPEAKER: Yeah.

JOHN PEPPIN, DO: You'd see the same thing with heroin, right?

HOWARD A. HEIT, MD, FACP, FASAM: Well, I mean, availability, availability. That there's a percentage, almost a fixed percentage that will use it. It's if you want to say alcohol, 14 percent in the United States, opioids 4 to 5 percent. It's a fixed percentage. I mean, genetics

plays a great role in addiction medicine.

MARTIN D. CHEATLE, PhD: And the thing that's interesting, though, because all of those opioid deaths, I think the average number of drugs on board it was 4.5. I mean, opiate was just one of them. And when it was opiates, they just put it in the opioid bin. They really need to talk about benzodiazepines, that are prescription drugs, and it's the combination that kills them, not just the opiates.

HOWARD A. HEIT, MD, FACP, FASAM: And how they collected the specimen, too.

ROB GATLEY, MD: Actually an interesting point with the parallel is if there was a cumulative increasing risk the longer you're on an opioid, the greater your chance of becoming addicted and the greater your chance of death, you'd think the curve for death and treatment would be steeper than the sales.

MALE SPEAKER: Yes.

ROB GATLEY, MD: So it looks more like it's an acute problem that affects a certain percentage.

MALE SPEAKER: Well, that's a point.

HOWARD A. HEIT, MD, FACP, FASAM: It would be real interesting to put the sales of benzos on that.

NALINI VADIVELU, MBBS, MD, DNB: Yeah, benzo.

MALE SPEAKER: That would be real interesting.

NALINI VADIVELU, MBBS, MD, DNB: With the

buprenorphine, I was reading about it doesn't need that (inaudible) benzo and buprenorphine, you know?

MALE SPEAKER: That started in New Zealand when it first came, New Zealand and Australia.

NALINI VADIVELU, MBBS, MD, DNB: So this is very important, what are the other drugs they were taking. Is this death is just only due to this drug?

NEIL SHUSTERMAN: This is the CDC information that everybody's seen that. It came out in 2011 I believe, or early 2012. No, they've been on this hobbyhorse, as well, beating the drum.

HOWARD A. HEIT, MD, FACP, FASAM: I notice they call them painkillers. I mean, pejorative term right in the title, right?

MALE SPEAKER: (inaudible) [Laughter]

MALE SPEAKER: I don't think that was on there.

[Background Conversation]

MALE SPEAKER: When they use the word "painkillers" do they really mean opiates or do they mean the NSAIDs, acetaminophen? Are they included in that?

NEIL SHUSTERMAN: This is their title.

MALE SPEAKER: I understand that, but when they decide what drugs to put in here.

NEIL SHUSTERMAN: So I thought this is where there is at least one opioid in the mix.

MALE SPEAKER: But you're absolutely right, and we do notice the term knocked around.

MALE SPEAKER: NSAIDs wouldn't be part of that.

NEIL SHUSTERMAN: That was intentional, obviously.

MALE SPEAKER: Yes.

GAVRIL W. PASTERNAK, MD, PHD: If you ask the average person if Advil's a painkiller, they'll say yes.

MARTIN D. CHEATLE, PhD: But again, it's misleading to practitioners when you say this is opiates because that's what they think. And then people who need opiates don't get them because the doctor's so afraid. If you said, "No, no, that was a polydrug death," then it's a little bit different territory.

NEIL SHUSTERMAN: Anyway, I went through this about the crush-resistance. The key point here is this was approved at the end of 2011. Interestingly it got hung up at the FDA for a year for nothing to do with the actual application, but something to do with another part of the FDA. So those of us who kind of believe that, that this could be valuable, have been distressed during 2011 as we saw OxyContin being harder to abuse and Opana being features on *USA Today* and being called the new, superpotent OxyContin and all that. But it was launched in February of this year.

So here's the physical characteristics that make it unique. The original Opana, and this is hardness measured

in newtons unit of force. It just needed a force of about 100 newtons to crush it. A human single bite can get up to about 550 newtons. And the new Opana we claim to be at least 1,000 because the formal testing equipment that we can make a claim on with the FDA only goes up to 1,000 newtons. But we struck it with a hammer, which we have measured as 5,000 newtons, and it's not crushable by a hammer either. So the stuff is hard.

GAVRIL W. PASTERNAK, MD, PHD: Does that change if you freeze it?

NEIL SHUSTERMAN: No, that's not changed if you freeze it. I don't know, people saw it here. So what happens with that cut rod, it then goes into a machine that cuts it into individual tablets. It comes out of the extrusion process as that rod. And then obviously the length of each tablet is its height. So, it is hard.

During the preapproval process for this formulation, we did some work at Columbia, where we had experienced individuals, those who routinely snort opioid products for recreational purposes, in a crossover study manipulate both forms, the old Opana and the new Opana, before we submitted it for FDA approval. And obviously they didn't have a lot of time to think about it in advance, but the lab virtually anything that they asked for to try to manipulate it. They manipulated 28 of the new tablets, so

these are actual instances, and 25 of the old.

And what they found at the end of the day is that the overwhelming majority of instances, they were able to reduce the old to a powder. They were not allowed to actually snort it, and very infrequently were they able to reduce to anything but crumbled little pieces at the most. Which, as you can see here, "Would you be willing to snort the material?" In all instances they said yes for the old, and an extremely reduced percentage gave the same answer. That's actually one out of 28 gave that answer for the new Opana. So going into our submission to the FDA, we were generally optimistic that what we intended it to be able to prevent, it was going to do that.

I have to put up the important limitations here of the data. The most important limitation is that these are observational data. So they're surveillance data. They weren't derived from studies specifically designed to answer the question whether abuse levels have been affected. And the time frame is relatively short. I'll be showing you six to nine month data because that's the length of time it's been out on the market, relatively low number of observations. And because during this time old Opana was kind of coming down out of the supply chain and new Opana was coming up, there hasn't been obviously stabilization of the prescription data because both were circulating at the

same time.

So with those limitations, let me go through the sources. I think a lot of people here are probably familiar with both Inflexxion, which has the NAVIPPRO System, and RADARS, which has a number of systems available. We subscribe to their drug diversion information, which is from the law enforcement side, and the poison center information, which is the intake reports from 50 of the 57 poison control centers in the United States. So they provide complementary views of the data, and the NAVIPPRO information comes from addiction treatment center intake information.

The reason to show you this is because this illustrates the overlap period. So the new formulation was introduced in February. We now at the retail level, 92 percent of Opana that's going out a retail pharmacy door is the new formulation. Personally I'm a little surprised that there's still a little bit of the old formulation around, but that's what IMS data appears to show. And during the majority of the year, we were coming up and the old formulation was going down.

And then I superimposed here the periods of observation I'm going to show you. So the RADARS will look through June 30th of this year. And the NAVIPPRO data, so NAVIPPRO first put images of the new Opana into their system on April 1st, so basically they weren't able to

differentiate between the old and new before that time. But actually since their system is online and a little bit more real time, they were able to give us data through September 30th. So you'll see these data from the two sources, and that gives you kind of a reference point of what we're talking about.

Okay, let's look through the NAVIPPRO data first for total level of abuse. The NAVIPPRO System represents a national program of surveillance of substance abuse through recording of information from the ASI-MV, Addiction Severity Index-Multimedia Version, which is the intake questionnaire that's used in a number of addiction treatment centers throughout the country. Please bear in mind this is not a probability-weighted sample. In fact, it may not even be generalizable to the entire population, as I'll show you in the next slide. But it does provide important information in a sensitive population at high risk for prescription opioid abuse.

So everybody who comes in gets these screens, and they're asked to indicate what substances they've taken in the last 30 days, and that information is then recorded, becomes part of their treatment file at their treatment center. But it also is uploaded in an anonymous, HIPAA-compliant fashion to Inflexxion.

And what we're showing here is the fact that old

Opana used to be octagonal. New Opana is round but has a biconcave form. And then there has been two strengths of generic extended-release oxymorphone on the market this year, 7 1/2 and 15 milligrams. And then this is Opana IR. So not only do the pictures come up so they can choose, but there's also sort of false positives and false negatives, so there's fake images, as well, to sort of calibrate how well the individuals are actually filling out the information.

So, overall throughout the country there's about 506 sites that use the ASI-MV. During the period of time we're talking about here, 396 of those sites were active online and able to supply information. Because the upload process of new information depends on the site doing it, not all of them were on board at the same exact point in time, and some were coming on board later in the process or some were dropping out of the information.

Here's the distribution of the centers around the country. You'll see that there's a notable spots that are not included, Kentucky and West Virginia being two of them of note.

M. CARY REID, MD, PHD: Something about the distribution that's interesting, there are many states not represented at all. Why might that be?

NEIL SHUSTERMAN: Obviously addiction treatment centers subscribe to this service, so whether they have

chosen not to use it or to use it is a totally business-driven decision I would say or a voluntary decision. And I guess this point also. 68 percent of all the assessments came from five states.

And this is the number of assessments. So if you look through 2011 when the only formulation of Opana that was circulating was the old formulation, there were 70,000 total assessments done. And there are less here because these are quarterly assessments. This is a rolled up number, obviously, you can see that, through the first three quarters of 2012. Of this larger number, anybody who reported any opioid abuse, so this includes all abuse, both illegal and legal, and this all substances, so benzodiazepines, amphetamines, whatever is in the top number. But if they said any of the opioids, it rolls down to this number on this row here.

So you need to be able to express the information in some kind of rate form to allow comparisons from one period of time to another. And what they've been using in the NAVIPPRO System is dispensed prescriptions during that time. So, interestingly the two formulations have different NDC codes, so we can actually track with a high degree of precision which formulation from prescriptions are actually being dispensed. So that gives us the specificity in addition to the actual identification of the tablets to

separate the old formulation and the new formulation in the data. So this is where the current information is, and that's where we get the 91, 92 percent versus the 8 percent for the old versus new.

This is a plot over time of reports of past 30 day abuse per 100,000 prescriptions dispensed during the same period of time. So for the old formulation, designated OF in blue, the new formulation, designated crush-resistant, CRF, and I'm going to say this is projecting as green. Sorry, sorry. Yellow. And the generic oxymorphone in green, which is available in the 7 1/2 and 15 milligram strengths in 2012.

So here's sort of the baseline. During all of 2011, 89 per 100,000 prescriptions dispensed reports of 30-day abuse of the original Opana. And then you see as the new formulation came on board in the second quarter that the rate, either compared back to this rate or compared to the concomitant rate of the still-circulating crushable Opana is shown there. I'd be very careful about these later quarters because that's when the number of prescriptions dropped very low, and you can see the confidence interval around that number has ballooned out. But there is evidence here of a reduction in abuse in the time period under observation.

GAVRIL W. PASTERNAK, MD, PHD: What percentage of the market is generic as opposed to Opana?

NEIL SHUSTERMAN: Randy, what would you say?

RANDY: About 10 percent.

MALE SPEAKER: Is generic?

RANDY: Yes.

NEIL SHUSTERMAN: In those two dose strengths.

MALE SPEAKER: So in absolute numbers, even with the new formulation, still much more of the abuse comes from Opana than it comes from the generic.

RANDY: No, that bar is the old formulation, right?

MALE SPEAKER: Hm?

RANDY: The blue bar is the old formulation.

NEIL SHUSTERMAN: Yeah, the blue bar is the old from.

MALE SPEAKER: [Crosstalk] times 61, right?

RANDY: Wait, your question was what percent of the market is generic? That's what you asked me, right?

MALE SPEAKER: Right.

RANDY: So all oxymorphone currently about 10 percent of it is generic extended-release oxymorphone 7 1/2 and 15.

MALE SPEAKER: Right. So that means that the rate 61 for 90 percent of the oxymorphone sold because the old stuff is being pushed out, which means that you have to either multiply the yellow by ten or divide the green by ten for a relative total amount, not percentages.

RANDY: These are relative. They're rates.

MALE SPEAKER: That's per 100,000.

RANDY: It's already (inaudible)

MALE SPEAKER: If you've got ten times -- okay, never mind.

NEIL SHUSTERMAN: I think the other important point is because the generic is relatively low, again the confidence intervals are pretty wide. But the trend here and the suggestion that leaving crushable products out on the market could be presaging a yet even greater problem I think is what the data could be suggesting.

HOWARD A. HEIT, MD, FACP, FASAM: Do you think there was a rush to abuse it in the end?

NEIL SHUSTERMAN: Yeah.

MALE SPEAKER: In third quarter '12, use it or lose it.

NEIL SHUSTERMAN: Oh, you mean for the old Opana?

MALE SPEAKER: Mm-hm.

NEIL SHUSTERMAN: I don't know if this represents material that was hoarded.

MALE SPEAKER: Right. And patients hoard.

NEIL SHUSTERMAN: Yeah. Somebody went to somebody's cabinet and found it late in the year, so it was available and reported that as such. All I know from our actual data is that there still is crushable Opana in the retail

channel, at least as reported by IMS, because there's about 8 percent still being dispensed at the retail level.

MARTIN D. CHEATLE, PhD: You know what would be interesting is to plot in all those the abuse of heroin, and I bet that went up.

NEIL SHUSTERMAN: Well, so that's obviously the Sisero[sp?] article or letter to the editor in the *New England Journal* and some other indicators. The NAVIPPRO group recently published on the oxycodone data looking at heroin use and suggesting that that has not gone up. But I think that is not at all by any stretch of the imagination a settled issue. I think that's still quite an open issue about what's happening. Because there probably are pockets of different availability, and I think that's around the country there is variability on that point.

MARTIN D. CHEATLE, PhD: The overall trend, since people have been more frightened to prescribe opiates, opiate prescribing goes down, heroin goes up. Overall, not just the tamper-resistant. The docs say, "I'm afraid of prescribing opiates." So if you go by a region and the opioid prescriptions go down, heroin goes up. They just shift their addiction.

HOWARD A. HEIT, MD, FACP, FASAM: I think that that also shows when new Oxy was introduced in Canada, the deaths from new Oxy went up because they couldn't get at it and

couldn't get high, and so instead of taking one and chewing it, they took three and swallowed it to try to achieve the same clinical effect.

NEIL SHUSTERMAN: So another way of looking at it, that was longitudinally over that period of time. But NAVIPPRO summarized the data in chunks of time. So looking what we're calling the before, that's not accurate. This represents what I'm going to say is the old formulation, and because we have longitudinal data, this is looking at it all the way from July of last year, which is for some reason cut off on this graph, going all the way out to September. But the new formulation came on board in the system in April, so that's April to September.

And again, corrected for prescriptions by 100,000. And here's the overall statistic that we have used to generate this number of a 59 percent reduction over this time period. And on an absolute basis, you can see where the generic low dose strengths, because they came on board early in the year, also still exist.

The ASI-MV also records route of abuse, so this allows us some specificity in terms of understanding our specific problem. So this is what Matt was referring to before. This is sort of the fingerprint of each abused substance. And for oxymorphone you can see far and away nasal inhalation is the predominant route of abuse, followed

by intended route of administration, which is obviously oral swallow, and then intravenous and other routes. Intravenous is here. Chewing and other routes, rectal or whatever, are there.

So how did the new formulation impact this distribution of route of abuse. You saw, I showed you for the old formulation it was about 77 percent. That's dropped down to 20 percent. Based on how the formulation was intended to perform, what we showed in the small number of individuals who tried to manipulate it before it was approved, it would appear at this point in time that in the real world, it's trending in the same direction. It's hard to crush, and people are unable to insufflate it nearly as frequently as they were with the old formulation.

So I said both formulations had a gelling agent, and this shows that we haven't inadvertently increased a different form of abuse, i.e., injection, with the new formulation. So they're both about the same, and obviously we're not claiming any change in that.

Switching to the RADARS data. This adds a complementary data screen. So people familiar with RADARS know that it captures de-identified prescription drug abuse, misuse, and diversion data for specific products using 3-digit zip codes to be able to localize it throughout the United States. And then they calculate rates based on

population, as well as drug availability in those 3-digit zip codes. This is captured through 50 of the 57 US poison control centers, so it has a high representation of the entire United States. But since most people usually will call a poison control center by phone, it doesn't have as much of the visual specificity that the ASI-MV data has, so bear that in mind. And in the data I'm going to show you here, they did not separate out between old Opana and new Opana during the period that I'll be showing you.

A separate stream of information is based on a collaborative effort with the National Association of Drug Diversion Investigators, NADDI, where they monitor new investigations opened up by 300 prescription drug diversion investigators from law enforcement across the country. They are surveyed quarterly and asked to report what new investigations they've opened for which drugs.

So this is the coverage of RADARS. A few pockets of missing states that have not yet signed on board. Richard Dart, who runs the RADARS program actually has told us that he's pretty close to getting that number 50 up significantly higher, so 53, 54. I don't know if they'll ever get all 57. It requires additional work from the poison control centers in capturing during the intake phase. So obviously in a cost-constrained environment, amount of resources makes it a little bit challenging. But it's pretty good coverage. And

the drug diversion, obviously 300 investigators doesn't cover the entire United States, so the red indicates where they have investigators who are sending in information.

This is actually interesting because they're also monitoring data for OxyContin during this time period. And they've divided time into three epochs: the period of time when OxyContin was crush-resistant and Opana wasn't, and then the period before that, the period during that, and the period where we were both crush-resistant. So let's see how that looks. They used two denominators. I have both available but for the sake of saving time in the presentation, and they both show the same thing, I'm going to be showing the data, which is sort of like prescription data. Here they call it per 1,000 unique recipients of dispensed drug. This is all derived from IMS data.

Here's what I was talking about in terms of the time periods. Prior to the third quarter of 2010, what was actually available was crushable forms of both drugs. And what you see here, the blue dotted line represents the overall rate averaged over that period of time. So somewhere around .7, .75 exposures. This is how they expressed their data, per 1,000 unique recipients of dispensed drug.

After the new OxyContin is introduced into the marketplace, you can see that the Opana rate jumped by 35 percent to this figure here. And then if you look at their

data presenting at the end of the second quarter, so this is June 30th, you see from the peak to down here there's a 35 percent reduction. This phenomenon is kind of interesting because this suggests that individuals will move to whatever is the path of least resistance in an environment where maybe their drug of choice was constrained. And that's I think invariably caused the squeezing the balloon effect or other analogies to that.

A similar pattern was shown with the drug diversion program. They don't go as far back in time, so they can't separate it into those three periods. But over basically all of 2011, comparing that rate to the rate in the second quarter of 2012 is about a 45 percent reduction.

So these are obviously early data. They need to be confirmed by additional observations over longer time periods. But they certainly go in the direction that we postulated when we developed the formulation and then had it approved and introduced it in the marketplace. And at the same time, there is a potential worrisome trend that leaving crushable generic oxymorphone out on the market could be recapitulating the problem that actually existed before. What I didn't show, or I think I did, is that for generic oxymorphone, its major route of abuse is back to snorting, as well. So, questions, observations, reflections?

HOWARD A. HEIT, MD, FACP, FASAM: I have a

question. Why your company, Purdue Pharma, do not get together and make clear why generic companies are getting a free ride with all these drugs as they come on board, as far as abusability. Because what happens, there's OxyContin now generic being introduced again in Canada. It seems that the generic forms get a free ride, both in cost, programs, education. And do you folk go and point that out I presume to the FDA?

NEIL SHUSTERMAN: Not to go too far off course, but both Purdue and Endo have filed citizens petitions with the FDA in terms of asking them to reevaluate their policies towards this particular class of drugs and crushable versus noncrushable, and the role of what some people call abuse-deterrent formulations, crush-resistant formulations, whatever lingo you want. How the FDA is going to rule on that, and they have a lot of their own issues to contend with.

Because obviously there's a bunch of generic companies out there saying, "Hey, health care costs are high. We need generic formulations in the United States. These are the rules that we got our drugs approved." So it's going to be an interesting review by the FDA where they eventually land. You're quite right. There was a lot of provincial input to Ottawa asking the Canadian Health Canada not to approve the generics. And they said, no, they met all

the requirements.

MALE SPEAKER: And they're presumed that the generic has a greater market presentation secondary to the cost. I'm just presuming that.

NEIL SHUSTERMAN: Well, that's what happens obviously in every other generic introduction, right?

MALE SPEAKER: Yes.

M. CARY REID, MD, PHD: A question on the Addiction Severity Index. The numerators are from individuals who are treatment-seeking, right?

NEIL SHUSTERMAN: Well, they could be seeking or they could be court-appointed, so it could be voluntary or involuntary.

MALE SPEAKER: But non-treatment-seeking we don't know.

NEIL SHUSTERMAN: Right. I think anybody who attended or followed the FDA's advisory committee back in the end of 2010 heard about the various limitations of the data sources in the United States, SAMHSA data, DAWN data, these sources. There's no perfect data source.

M. CARY REID, MD, PHD: right. But the trends are moving in the direction you want them to move, or they certainly suggest.

NEIL SHUSTERMAN: Yes. We much prefer to be part of the solution than the problem. Okay, thank you.

MATTHEW WIEMAN, MD: Thanks, Neil.

[FILE 5]

Oxymorphone in Pain Management

MATTHEW WIEMAN, MD: All right, pretty much officially the last section here. I think we've had again a lot of really good conversation. So I'm going to ask some very specific questions now to kind of pull some things together. Obviously we have so many ideas that have come out, which is great, that we're going to get back to some of those a little bit later. And I'm going to reach out to each one of you to discuss some of the things that you were each interested in, as well as of course finalizing the summary of what came out of today.

But now's the time for some of the straightforward brass bolts of me asking you what we can do for Opana ER, taking in all the discussion that we've had, to push this forward clinically over the next several years as short term, medium term, long term. And yes, some of them are going to be the classic pharma questions, but we do have some very specific ideas, too, that we wanted to run by you and gauge how interested you were in those topics, and also get some specific feedback is it important to you, is it not, how would you like to see it, do you have any other kind of comments.

And then when I'm done with that, Rob is going to

kind of finalize some things that you all brought up that isn't specifically on our list, as well. So the system that we talked about, things that are a little bit broader, but we wanted to get some real detailed numbers from you guys for answers about Opana ER.

So one of the thoughts really is kind of the basics. We did talk about this, but it was tough to get too many direct answers. Are there a set of patients that you folks do use, and I know you may not, but do you find there are some patients that suit this drug? Is there a disease state that you find, or is there a setting? It just helps us focus on where it's currently being used and where there might be ideas. You had said in your area it's in that palliative care, it's the last.

NALINI VADIVELU, MBBS, MD, DNB: The typical patients would be people who have already taken opioids before, so they're non-opioid-naive. That would be the typical patient. Disease states I'd say cancer. And then the care settings that we're using right now, the inpatient setting.

MATTHEW WIEMAN, MD: That's perfect. Thank you very much. That's the kind of thing we need to build on and find out where to go next. I'm just going to kind of put people on the spot if you don't mind.

PATRICIA BRUCKENTHAL, PhD, ANP-C: In the

outpatient noncancer population. So currently it's not the go-to drug. Part of that's cultural and history, so it wasn't the drug that I was trained on. And then the other part is access to it.

MATTHEW WIEMAN, MD: That's great. The reason and the answers. That's going to help us. Great.

PATRICIA BRUCKENTHAL, PhD, ANP-C: But I have used it anecdotally. And again, the one or two cases or few cases that I can recall, I mean it's an effective drug, but that's an anecdotal answer. But I've tried it on patients and then they can't access it. And our population is primarily musculoskeletal.

MATTHEW WIEMAN, MD: Musculoskeletal.

PATRICIA BRUCKENTHAL, PhD, ANP-C: Primarily. I mean, we have others.

MATTHEW WIEMAN, MD: So are you similar? Is it towards the end, or does it ever occur to you to use oxymorphone in the earlier setting, earlier on before they've tried all the other drugs?

PATRICIA BRUCKENTHAL, PhD, ANP-C: Only after I've recently seen my rep.

MATTHEW WIEMAN, MD: All right. Impact apparently. And then settings, you just described.

PATRICIA BRUCKENTHAL, PhD, ANP-C: That's the only setting I work in.

MATTHEW WIEMAN, MD: Great. Could I ask you?

M. CARY REID, MD, PHD: Sure, so palliative care and out in the primary care world. I think the answer is I use it sparingly, probably because I wasn't trained in a situation where it was used. In the limited cases where I've seen it used, I think it's effective. I will leave the meeting with the better appreciation for its value in geriatric patients. I think that may be a niche to focus on.

MATTHEW WIEMAN, MD: Okay. And any ideas that come up, now that you've heard these things. Thanks very much.

RONALD J. TALLARIDA, PHD: I'm not a physician, but I'm oriented toward preferring oxymorphone over that because it is a secondary, it's a product of oxycodone.

MATTHEW WIEMAN, MD: Okay, so you like that.

RONALD J. TALLARIDA, PHD: I like that, and I think that accounts for its potency and it has therefore I think a more specific spectrum of action.

MATTHEW WIEMAN, MD: All right. Is there any information that might help us get further along with this?

RONALD J. TALLARIDA, PHD: Not off the top of my head. It's certainly something I'd like to think about, yes.

MATTHEW WIEMAN, MD: No problem. How about yourself?

MARTIN D. CHEATLE, PhD: I don't prescribe. But in the university-based pain clinic that I work in they mostly

use methadone and OxyContin. In the community I have seen more use of oxymorphone for some reason. I don't know why.

MATTHEW WIEMAN, MD: Are they with more complicated patients? I mean, you're probably dealing with pretty complicated patients, anyway.

MARTIN D. CHEATLE, PhD: I think it's just more the sort of opinion of the person who runs the clinic. They just feel that methadone should be used, and they know how to use it, and it's low abuse potential, and it's cheap. And that's their belief.

MATTHEW WIEMAN, MD: All right. And I'm hearing this. I mean obviously right off the bat the first four folks have mentioned that they weren't trained on it and they don't really have access to it.

MALE SPEAKER: But you have to highlight why it's different and why it's superior in certain cases.

MATTHEW WIEMAN, MD: Of the few things that we've mentioned, any of those the most important to you?

STEVEN P. COHEN, MD: I think the geriatric component is important. There's more and more people that are living longer that if you can sort of highlight that it's maybe a safer drug in terms of fall. That would be probably my primary one off the top of my head.

STEVEN P. COHEN, MD: I can think of a couple of scenarios, and I'll go over them. But I think it's also

important to recognize that it's like NSAIDs. I mean, one is not superior to another, and they recommend that if you try one drug, I mean, everyone recommends it, and it doesn't work, then you try another drug. So there are some differences, but the similarities far dwarf the number of differences.

So the advantages would be IV, sustained release, abuse-deterrent form, or TRF, tamper-resistant, and then an immediate-release. So like for the OR, patients who perhaps are opioid-naive but will need opioids after for a period of time. Elderly people with like hip or knee replacements who are going to go to rehab, and they often end up on opioids. Another thing is like I said, people, even though they'll be tried on one opioid, they won't stay on that. And they may be on opioids for years, but they won't stay on one particular drug for the rest of their life because they'll develop whatever it is, tolerance. And because of incomplete cross-tolerance, they'll rotate opioids. It could also be a good choice for opioid rotation.

MATTHEW WIEMAN, MD: And just to put mine out there. I always saw that the irony in that is that we're again trying to find a patient that's perfect for it. And I say this when I'm talking internally as well. The same reason that it's potentially a good idea for patients that are uncomplicated, young, starting this out, might be on it

for a longer period of time is the same reason that you find it probably a good thing for the complicated patients: kind of its lack of interactions, its long half-life.

So that's why we ask these questions. Because it's a pretty difficult job to create the science that's going to be most interesting to the clinicians when the drug is what it is. And it has a lot of great attributes, but it's hard to find an exact patient because it quite honestly may be good for a variety of patients. So that's why we're trying to -- yeah.

RONALD J. TALLARIDA, PHD: Do you offhand know the IMS data on prescriptions for this drug versus others? I'm curious to know where it stands.

MATTHEW WIEMAN, MD: Do we have that kind of data?

Randy: Well, I can verbalize it for you. If you look at the entire kind of long-acting opioid class, probably about 30 percent of it is morphine sulfate extended-release, about 30 percent or so is OxyContin. Our market share of prescriptions is about 4 percent. So, 30, 30, 4, and then you have a mix of other things: Nucynta, Kadian, Avinza.

MALE SPEAKER: So you have 4 percent [Crosstalk]

MALE SPEAKER: Extended-release

[Crosstalk]

MALE SPEAKER: Fentanyl I didn't mention, but

fentanyl has a big chunk of that, as well. I'm not sure what the share is.

MARTIN D. CHEATLE, PhD: The other thing, this truly is a unique molecule metabolite. I mean, that's another advantage is that if you have someone who's high risk, and it's an abuse-deterrent formulation, and you can monitor them uniquely for that metabolite. That's something that should be emphasized.

MATTHEW WIEMAN, MD: All right, thank you. That's a good point.

MARTIN D. CHEATLE, PhD: So you stratify high risk. Well, the urine drug screen, it just says opiates, yes or no. And so that's not good enough necessarily.

MATTHEW WIEMAN, MD: That's a good point. Thanks. Dr. Smith?

HOWARD S. SMITH, MD: Nothing new. I, like a lot of the people in this room, see patients that have already seen other people in the community and so forth, and so by the time I see them, they've already been tried on many opioids. And so they are on a double-digit amount of medicines, and so the lack of CYP interactions is of significance, without having drug-drug interactions. And the fact that the potency is high is also a consideration.

MATTHEW WIEMAN, MD: Great, thanks.

CHRIS HERNDON, PharmD: I guess there's two

different points. One is where I'm using it now, and that seems to be primarily in some of our patients that have been put on opioids, whether rightfully so or not, and have become tolerant and tolerant quickly to whatever agent they're put on. I've tended to have good luck if they're not candidates of methadone, especially if there's a lot of cardiovascular baggage. So that tends to make up half of the people we have on it now. And the other half are the folks that, "Well, I'd like to try you on this drug." "I'm not taking that. That makes people die." You know, for whatever media perception that they've gotten over the years. And so hardly any of the patients that I see that are legitimate pain patients have heard of this, and it's not, "I saw a documentary that they give morphine to people who are dying, and I'm not going to take OxyContin because everybody's abusing it, and methadone is for heroin addicts."

You know, everybody has their own preconceived notions. But I haven't seen the dose creep, and so the patients who Vicodin worked great and now it doesn't. And then we went to the next thing, and that worked great, and it lasted about a month or two. They seem to be a little bit more stable on oxymorphone.

MATTHEW WIEMAN, MD: Okay. And any other suggestions about where to go with this, besides what you just said.

CHRIS HERNDON, PharmD: You mean data I'd like to see?

MATTHEW WIEMAN, MD: Yeah.

CHRIS HERNDON, PharmD: I'd love to see data in obese patients specific to some of the big push-back we get with like the fentanyl is changes in body weight and habitus and the kinetics of the drug.

MATTHEW WIEMAN, MD: Distribution?

CHRIS HERNDON, PharmD: And distribution. I'd love to see specific data on changes in sleep disordered breathing with this versus some of the others. And another thing that I don't think we have is, like we talked about yesterday, what happens to these medications when you take them orally in patients that have had bariatric surgeries of different types.

MATTHEW WIEMAN, MD: Gotcha. All right, thank you. That's great.

JOHN PEPPIN, DO: I base my prescribing on the quality of the lunch brought by the rep.

MATTHEW WIEMAN, MD: All right. Well, that's clear. That's easy to handle.

JOHN PEPPIN, DO: Actually, I mean this isn't available to me just because I work in the hospital. But I have prescribed it for patients in Kentucky and also in Iowa. You know, it usually was the patient who had failed

other things, I wanted to keep the least divertable and abusable number of units available, which is another benefit.

MATTHEW WIEMAN, MD: Yeah. Well, there is data that shows most patients do take two to three OxyContins a day as opposed to two Opanas in one of the studies that we have. So that's interesting. That could also be an interest going forward with reimbursement and limits on numbers.

MALE SPEAKER: Typical patients will be just about anybody with chronic pain, except for fibromyalgia.

MATTHEW WIEMAN, MD: Okay. And I'm going to get some more specific questions after we go to the next one. I'll skip Neil because I know what he's going to say.

NEIL SHUSTERMAN: I don't prescribe.

MATTHEW WIEMAN, MD: Yeah. Dr. Marlowe.

KAREN F. MARLOWE, PharmD: Patients our residents are using it with or I'm suggesting it to them are typically it is their second or third agent. And it typically is those patients that have had multiple intolerances. And a lot of times we're using it in patients with chronic pancreatitis, we're using it in patients with sickle cell. They list multiple allergies. They've had problems with morphine.

They've had problems with OxyContin. They won't ever try them again. It's not that they failed them for pain reasons. They've got other issues with them. And our issue

is getting it approved, getting them on it. And a lot of my patients are either Medicaid or self-pay, getting them qualified. And then if I can get them on it, they'll usually be successful.

MATTHEW WIEMAN, MD: So it sounds like some of your patient populations are specific. Would it be of any value to you to have a study, knowing that it is an opioid and likely you're going to see an effect, but will it be of value to you to see some basic data on that specific area, say sickle cell patients and Opana?

KAREN F. MARLOWE, PharmD: Extremely helpful. I mean, their pain we know is different. It's a mix of bone infarction and a mix of skeletal muscle pain. It's very different, and so for them, their response rates. Plus they have a psychosocial aspect that's very distinct, especially the adult sickle cell patient. So when you put that stew together, they respond very differently.

MATTHEW WIEMAN, MD: Okay. It's a nice avenue. What about yourself?

NALINI VADIVELU, MBBS, MD, DNB: I had a question. The ER, like have they ever given it like three times a day?

MATTHEW WIEMAN, MD: I'm sure it has been. We haven't studied it at three times a day. The dose is twice a day, but of course anecdotally I've heard it being used in different --

HOWARD A. HEIT, MD, FACP, FASAM: I think one of the things, in outpatient medicine it's how much time you have to spend in writing the prescription. So is it on the formulary and what tier it is and what expense it is to the patient. So that's I think a number one issue. Number two, as far as putting on an addictionologist hat, is I wonder if the amount of Opana, that is number of pills per month, compared to the number of pills of morphine or OxyContin is less. Because if you could show in a study that you're prescribing less pills, that means there's less to be abused or diverted.

MATTHEW WIEMAN, MD: Good point. And we have that data actually.

HOWARD A. HEIT, MD, FACP, FASAM: I think that's really important. Because I know in my practice I do pill counts. I give enough medicine from appointment to appointment plus three days. He can't use those unless you call me first. And so it makes my life easier if I could use one pill twice a day as opposed to whatever.

MATTHEW WIEMAN, MD: Sure. And Todd, what was the name of that study?

TODD KIRBY: I published a bit on that. And what we looked at OxyContin compared to Opana ER, and we looked at comparable dose strengths in a chronic low back pain population, folks who had been on chronic opioid. So they

qualified by having been on opioids for at least two consecutive months in the osteoarthritis population and in the general population. So we did it without cancer. By diagnosis we did it all comers. We did it when they were both crushable. We did it after OxyContin became crush-resistant and Opana ER was still crushable, and we've done it since. And we saw about a half a tablet a day difference between the two.

MALE SPEAKER: Opana was less.

TODD KIRBY: Opana was less. Opana was a half a tablet a day less. And at the highest strength, if you took the 80 compared to the 40, you saw a whole tablet a day difference. After it became crush-resistant, OxyContin only went down to 0.45, still statistically significant. So the difference was maintained. And now that's been preserved again when they're both crushable. So if you think about not just doing a pill count in our practice, but if you think about some of the restrictions on the class that the commercial insurers are imposing or that the states are imposing, they're talking about an absolute ceiling for number of tablets in a month, then a DACON rate that's lower, daily average consumption rate that's lower, without conceding any quality of pain relief, might be of interest.

HOWARD A. HEIT, MD, FACP, FASAM: Yeah, because they don't make a distinction, let's say 120 tablets per

month by the insurance company, they don't make a distinction of 120 10 or --

TODD KIRBY: They don't care what.

MALE SPEAKER: -- which is ridiculous, or 40 80. And if you can show they use less pills per unit of time to treat X, Y and Z, I think that's important.

ROB GATLEY, MD: I think there was one reason it might not be promoted with that study was it was approached from the pharmacoeconomic situation. It's less expensive to cover Opana because there's fewer pills prescribed. The addiction end wasn't really the focus of that research. But to that point, one issue is the duration of analgesia. They're supposed to be twice-daily pills. I think those prescribing them know that OxyContin doesn't really last a whole full 12 hours.

HOWARD A. HEIT, MD, FACP, FASAM: Most people it doesn't. About 50 percent, it's a TID dose, the end of dose failure. What's the end of dose failure do you think of Opana compared to OxyContin?

MALE SPEAKER: Well, it much more consistently lasts the 12 hours.

HOWARD A. HEIT, MD, FACP, FASAM: I think that's a very important clinical point.

ROB GATLEY, MD: I think a problem with using that data to push the addiction message is the idea, well are

these extra OxyContin pills being diverted to abuse. You would have expected a drop in DACON after it became crush-resistant, and there really wasn't much of a difference. So the data makes it look more like it's a duration of analgesia question as opposed to a diversion question.

MALE SPEAKER: How much was the drop?

MALE SPEAKER: You're talking about drop in abuse?

ROB GATLEY, MD: No, in the DACON, the daily average consumption, that if there was m ore OxyContin going out because some was being diverted to abuse, then you would expect the reformulation to have made a difference. But since it didn't make a big difference, it's more likely just duration of analgesia.

PATRICIA BRUCKENTHAL, PhD, ANP-C: But still from a public policy standpoint or a public perception standpoint, the unit dose per period of time makes a difference and sends out a reaction. So I think it's an important point. I had a horrible interesting experience with our district attorney's office. It didn't matter if you were to talk about patient outcomes and dosing, and if 240 doses of something was equal to 60 doses of something else, and somebody got analgesic effect from it, that wasn't what was driving the issues on the table at the point. It was the doses that were available per period of time. And horrified. They really didn't understand the clinical aspect of giving

out 120 doses in a month period or 240 doses because the availability of that being on the street, or potential.

HOWARD A. HEIT, MD, FACP, FASAM: It's also human nature that if the pill box is filled this much, "Oh, if I take a couple extra, no big deal because I've got a lot left." I mean, I've heard this 100 times. Where if I only have this much, then I'm going to be sparing when I take it, or take it more as prescribed, which patients don't do.

PATRICIA BRUCKENTHAL, PhD, ANP-C: So that might be an interesting, important information.

MATTHEW WIEMAN, MD: Okay. Dr. Pasternak.

GAVRIL W. PASTERNAK, MD, PhD: I don't have a whole lot to add.

MATTHEW WIEMAN, MD: That's okay. Whatever you have.

GAVRIL W. PASTERNAK, MD, PhD: I know our pain service is using it. I don't think they're using it as frequently as they do the others. I think it's a second-line drug. I'm not in a position to use it a whole lot myself.

MATTHEW WIEMAN, MD: Okay. All right. Just to keep the discussion going, I'm going to go to the next slide, but we'll have more of these in some more detail. So we basically just covered this because I said "What are the gaps that you have here?" And we got at least an idea from almost everyone in the room about what might help them move

forward. And some of those were specific that I'm going to get to now.

The barriers, I think we also covered these in general. We know that the number one barrier is having it available to you to prescribe. And then the second part of that, my understanding, you can tell me if I'm wrong, was the fact that it's just not something that a lot of folks are used to using in their training.

STEVEN P. COHEN, MD: So you have the same problem that like a spinal cord stimulator or radiofrequency or device manufacturers have. If a company that makes radiofrequency generator sponsors a big, expensive trial that shows that it's effective in this context, it's not really that beneficial to their company because you can use any one. There's ten other devices on the market.

So when people write guidelines for opioids, like for sickle cell anemia, central pain, neuropathic pain, they do it in classes. No one separates the opioid. They write "opioids" right? Second-line treatment, third-line treatment or first-line treatment in certain cases with IASP. So even if you do a study and you show that it's never been studied in this context, it doesn't mean that people are going to prescribe oxymorphone. They may still keep prescribing OxyContin or MS Contin.

So unless you do a head-to-head trial, but if I

were your company I wouldn't do a head-to-head trial because these drugs probably have very similar effectiveness or efficacy. So with doing these trials, this is the problem.

MATTHEW WIEMAN, MD: Yeah. You hit on exactly the issue about this is kind of why this discussion is being held is about that specific area, about doing studies in individual disease states. How much does it matter to you? On one side, it may not. On the other side, there's folks that feel that that disease state's different enough that it would matter to them. But this is the kind of conversation we need. So thank you.

And I'll hit on this now that we're here. Are there any other disease states that folks here, and I heard sickle cell, are of particular interest? Would you say, "Well, even if it says it works, it would be nice to have it." Or what's the value in being able to have a publication? It may not go into the PI. Something you could talk about. If you asked you could get some information on it, have a scientific presence. Is there any other disease state that comes to mind?

GAVRIL W. PASTERNAK, MD, PHD: Not specifically, but I think your point's well-taken about the fact that opioids are lumped. But in terms of disease states, if I were thinking about them, I would look for disease states that would expand the market. In other words, disease states

where the opiates are not widely used, where they may actually be appropriate and indicated.

MATTHEW WIEMAN, MD: Where there's a gap. That makes sense.

MALE SPEAKER: What would those be?

MALE SPEAKER: Well, I'll leave it to you guys. You're smarter.

STEVEN P. COHEN, MD: They've done them for central pain. They've done them for phantom pain. They've done them for back pain. They've done them for diabetic neuropathy. Raj compared TCAs to opioids in comparative effectiveness studies. I mean, then you're left with these conditions that people are going to be very reluctant to prescribe opioids as a class to. I know people don't even like using that term, functional pain disorders, but things like abdominal pain, pelvic pain, fibromyalgia.

So I mean, they haven't been studied for this and there's no evidence. But even if you show benefit, people are going to say -- it's like when Dan Carr was testing intranasal ketamine in patients and did fibromyalgia. People were like, "What? Are we going to use this in fibromyalgia really?" I'm sorry I keep using fibromyalgia as an example. I don't mean it. The F-word.

MATTHEW WIEMAN, MD: Sure. I can see that. So there is some slight difference of opinion. I understand your take

on it and that's kind of why I'm asking. But it is interesting to see. Even though we may not be able to make a claim, and I won't ask you but that's what we're going to try to figure out based on some of the comments here today as well, but is there any incremental value in saying, "No, we're not showing you that we're better than something. It's not a head-to-head. It's not ground-breaking that it works in eye pain. However, no one else has data to show you that it does. And since so few people understand this molecule, there may be some incremental value in that, and that's kind of what I'm looking for. But that's absolutely the debate that we have at the table back at Endo.

NALINI VADIVELU, MBBS, MD, DNB: You could think about migraine and cluster headaches and stuff. It's not really for opioids, but --

MATTHEW WIEMAN, MD: Because I'm taking, ER, but the molecule, you never know.

NALINI VADIVELU, MBBS, MD, DNB: It's very painful, right, migraine headaches?

STEVEN P. COHEN, MD: You will never get buy-in from neurologists for headaches. Because I'll tell you, we have a neurologist who runs our clinic, and these are his words exactly. "Opioids have a special place in health [hell for headache patients] (inaudible) patients."

MALE SPEAKER: That's more like myth than bias.

STEVEN P. COHEN, MD: There's definitely data that you can look at, and I can say we did this study. It made *The New York Times*. We looked at all the headache evacuees from Morocco and Afghanistan. There were about 2,000 of them. And we looked at things that were associated with return-to-duty. And opioids were strongly associated with not returning to duty. That's not cause and effect. It could just be these people had lots of other problems. They were depressed. They had more pain at baseline, you know, greater disability and so they complained louder. They were put on opioids.

But there's other data to support when they look at people with things like migraine and in three years or five years, most people will stay the same. Some people will regress. Some people would progress. And there was definitely an association with opioids and progression. So I don't think that that's even a winnable battle. I'm not a neurologist.

NALINI VADIVELU, MBBS, MD, DNB: I'm just saying that's one place where they haven't found (inaudible) with opioids.

MATTHEW WIEMAN, MD: I think I beat that one down. But there's a potential to have some ideas there. And believe me, that's the debate we have. They're all valid points.

Now we come down to, this isn't what I'm going to discuss next actually, because here are some very specific questions. One of the things we're thinking about doing is creating a higher dose. This goes to a couple of things. It goes to the fact that a lot of the patients that are chronic patients on Opana ER were on greater than 80 milligrams a day, so 87 milligrams a day was the average in our pivotal trial for experienced patients with chronic low back pain at the end of the trial. So this means that's more than two 40 milligram pills.

So convenience, the need for it instead of giving other multiples, the confusion we talked about before. It's relatively low-hanging fruit. There's risk of having the FDA not like us pursuing this angle, but do you think having a higher dose, knowing that information, so a 50 and a 60 milligram tablet perhaps, knowing that that is based on the data we know and also the fact that the pill number again is an issue nowadays, would that be of any interest to you? And I know it's a little difficult with folks that are not prescribing a ton of it right now, but what do you think about high dose? Is that something that makes sense: patient convenience, convenience for you?

MARTIN D. CHEATLE, PhD: I mean, it's generally a no-no nowadays. Everyone's talking about PROP and everything, having these set parameters, which is not based

on evidence, but most things aren't. So I think there's just his perception that higher doses are bad, and that's why they've sort of taken off higher doses of OxyContin. And so I'm not sure that's a winnable battle.

MATTHEW WIEMAN, MD: That's definitely one of the barriers right there.

RONALD J. TALLARIDA, PHD: That goes with what I was saying before about one advantage of combinations is that you lower the dose.

MATTHEW WIEMAN, MD: Mm-hm. And that would take care of less pills as well if you had a combination. Anybody feel different about the high dose, I mean as well as that opinion because that's definitely valid.

MALE SPEAKER: (inaudible)

MATTHEW WIEMAN, MD: So make it easier.

GAVRIL W. PASTERNAK, MD, PHD: And there you have a little bit of the fact that people are more understanding that they use high doses. But the doses that we use in cancer pain can oftentimes be much higher than the ones you'd use in just --

MALE SPEAKER: I've never quite understood.

MALE SPEAKER: What's that?

JOHN PEPPIN, DO: We're not dealing with a different physiology between pain in cancer and pain in other things.

MALE SPEAKER: I'm not so sure about that.

MALE SPEAKER: I haven't seen good published data.

GAVRIL W. PASTERNAK, MD, PHD: The pain from a cord compression is not the pain from just a sprained low back.

JOHN PEPPIN, DO: Oh, no, but I mean the mechanism would be neuropathic pain versus somatic versus inflammatory pain.

GAVRIL W. PASTERNAK, MD, PHD: They're never a single entity. But the bottom line is if you take a look at the doses of opiates we use in our patients. Rich Payne[sp?] set the record: 1500 milligrams of morphine intravenously an hour.

MALE SPEAKER: Actually I got close to that.

MALE SPEAKER: That's a lot.

HOWARD A. HEIT, MD, FACP, FASAM: He went to divinity school afterwards. [Laughter]

MALE SPEAKER: Actually that was when he was a fellow.

STEVEN P. COHEN, MD: Well, going back to Chris' suggestion, so specific disease states and then he was saying that maybe there's less tolerance. Right, I'm saying I agree that that may not be the case, but this is how studies get designed. Someone says, "Hey, when my patients are on Opana they don't escalate the doses." And so this would be something to look at. You can do a really quick

pilot to determine whether or not you -- And then of course look at specific disease states, and as you were saying, psychomotor, like you break your hip, that's a bad thing if you're elderly. It's very costly. People die.

MATTHEW WIEMAN, MD: Well, this leads into the next ideas were really kind of I'm thinking about high dose, and then I'm thinking about a couple of different studies. And one of the studies was actually looking at it in cancer pain. And one of the things that we were thinking about doing is actually looking at it in cancer pain in a head-to-head trial potentially versus morphine.

A small study. So there would be some limitation of risk based on the fact that these are cancer patients receiving their opioid experience. They're going to either now be on a larger dose or a long-term drug, what is the outcome. And again, with this study there could be a finding, a pilot study that could introduce new data.

Since it is in cancer pain, we have very limited data, certainly no randomized, placebo-controlled trials really with our drug in cancer. It is a kind of a disease state, but it also combines looking at it against the gold standard. There's more risk there, but there's a potential, because we know if you give enough -- but if we have something like morphine there to say these patients, even if they did as well, there's a chance for a win there to say

you shouldn't just consider this one drug. This drug works in this. Does that sound like something interesting?

KAREN F. MARLOWE, PharmD: My biggest complaint about those types of trials is that either those trials do not give enough demographic information for me to know how to use them, or they aren't selective enough in their inclusion criteria. So I'll read one of those trials and I can't tell how to use the information. So I'll look at it and I can't tell were they using it in neuropathic pain.

And this goes back to your comment. I don't know was it effective in patients with primarily cancer pain that was neuropathic in origin, somatic, visceral. And so, yes, it was effective, or it was more effective than morphine. But I don't know anything. Because cancer pain is so broad. And so if you all design it right, it'll be helpful, but it needs to either be specific enough to the type of pain or discrete enough into the patients are enrolled, they have metastatic bone pain or they have visceral pain or they're all breast cancer patients, it's metastatic. That would be helpful.

STEVEN P. COHEN, MD: I would argue the opposite. With this study, you're not determining efficacy, that you should have very broad criteria so that it's more generalizable. You want a lot of different practitioners. You don't want just the best. You don't want one specific

disease state. I mean, these are kind of the guidelines. But I definitely hear exactly what you're saying. It's hard. So how does this generalize to my patient? But they usually say that with more inclusive criteria that the generalizability is great. This is good for something where you already know that it's efficacious.

KAREN F. MARLOWE, PharmD: And I would agree if they get that, awesome. But if they only get one or two of each.

MATTHEW WIEMAN, MD: So perhaps we use this again to find out what happens in a more generalized way, and then see if there's any hits. Again, depending on the numbers. But we'd have to decide. There's going to be some inherent complexities in designing a study with cancer patients.

JOHN PEPPIN, DO: You could do double crossover, double-dummy crossover.

MATTHEW WIEMAN, MD: Now, would you be able to get patients into that? Okay.

KAREN F. MARLOWE, PharmD: Some of the palliative care trials and the dyspnea trials are double-dummy crossover on some of the inhaled opioids that have looked at this. They are very low numbers, 20,40 patients.

MALE SPEAKER: But it takes on a whole different meaning. We have to use senators and legislators, right, for double-dummy. [Laughter]

MATTHEW WIEMAN, MD: Of course, the placebo.

GAVRIL W. PASTERNAK, MD, PHD: I hear the politicians don't inhale. [Laughter]

MARTIN D. CHEATLE, PhD: But they use (inaudible) [Laughter] So a secondary benefit of doing some studies is you could increase positive recognition, where people say [Crosstalk]

MATTHEW WIEMAN, MD: Yes. We may not see giant "It's the best thing since sliced bread for a scratch of your cornea," which can be pretty bad. But, yeah, there's some more generalizable, some information. Because currently there's just a lack of information, especially about our product, as well.

And the next question surrounds all the studies. But the next study we were thinking about particularly was again how do you deal with that, trying to get the information, but going head-to-head and they're opioids, there's so much variability, you might just be able to hurt yourself. It may not do much but say something negative, which again we want to be transparent and open, but we don't want to necessarily conduct a study on purpose that's going to not have a fair chance of showing some kind of a result, or has a lot of detrimental potential.

So something that kind of mitigated that in one of our sessions we discussed potentially doing chronic low back

patients, opioid-experienced, that failed OxyContin. So you're looking at a group of patients which apparently a lot of folks here are prescribing anyway. But again, you're getting more data. It may not be mind-blowing, but there may be some hits in a smaller study that allow us to say, "Well, in fact you use it this way. It is a small study. We may go to a bigger study. At least we have a publication where we have a study that shows in this group of patients it worked."

MALE SPEAKER: How do you define failed?

MATTHEW WIEMAN, MD: The devil's in the details for that, how we do that.

MALE SPEAKER: I think there are multiple studies for that (inaudible) they have enough patients.

MATTHEW WIEMAN, MD: And that's more one of the disease states, so chronic low back pain. But why would we do that over again because we've done that and it's common? Well, the addition of the OxyContin. Because again, no one's really going to go head-to-head. You're never going to see a study head-to-head, so this would be close. That's what would make it unique is that you're seeing direct kind of fails.

MALE SPEAKER: You wanted to do that with the cancer study, right? You wanted to do a head-to-head.

MATTHEW WIEMAN, MD: Morphine we wanted to do,

yeah. The cancer study, we thought --

JOHN PEPPIN, DO: Because we don't care what happens to cancer patients.

MATTHEW WIEMAN, MD: Well, we thought it's a tough group to treat.

MALE SPEAKER: We don't care if they get opiate-induced hyperalgesia.

MATTHEW WIEMAN, MD: No, we care. We care about all our patients. The point is that the chances there are that we may do pretty well against a drug like morphine. So those two areas. Now, they apply across the board. So the next big question is outcomes. And this applies to all the studies. When you look at this stuff now, and you see the VAS, you see typical outcomes, or you even see your patients. We all are aware that things are kind of changing. And in reality how you treat your patients are can they get up, can they go to work, or whatever goals they have. So the goals are it's no more "Oh, great. They're a three, not a five or not an eight."

What other ideas for outcomes would make you interested in seeing some of these studies? And that's one of the ways to make some of these studies more unique, as well, is putting in some new outcomes that necessarily are more clinically relevant. And so that's open all the way up to things like, "Are your patients feeling isolated?" Are

there reported outcome measures that we can come up with that you care about sleep disturbance, depression?

I'm just throwing it all out there. Are there outcomes that you would like to see in some of these studies that we're thinking about doing? Because they could be put in, as we develop them, into almost any.

MARTIN D. CHEATLE, PhD: I would just say again, that if it's true that it's very specific and you're drug-testing, you can compare it to other drugs in terms of hit rates on your drug screening. So for example, if someone is given oxy-oxy or whatever, it comes back as opiate, yes or no. If you could say using this drug compared to OxyContin or another drug, that we have a better way of identifying people who are diverting or misusing. Because that's unique. I mean, if that's what you're saying.

MALE SPEAKER: The urine drug test that is totally negative opens up a differential diagnosis. It doesn't tell you that the patient diverted the medication.

MARTIN D. CHEATLE, PhD: No, but if you have someone on oxy base, for example, most people if they use urine drug screens, it'll just say opiates present or not present.

MALE SPEAKER: It'll say either negative or positive.

HOWARD A. HEIT, MD, FACP, FASAM: Right. So if this

drug is specific, like fentanyl, for example, I think you have to be very careful when you do a urine drug screen on fentanyl because a lot of them won't show fentanyl. So you're accusing patients of diversion when they really aren't diverting.

MALE SPEAKER: (inaudible)

MARTIN D. CHEATLE, PhD: Not unless the lab test is directed at that molecule. And they're getting more sophisticated. But again, it's knowing the strengths and limitations of your test, whether it be a point-of-care or laboratory test.

MATTHEW WIEMAN, MD: Okay. So involving urine drug screening, and again the details to be worked out in each of the different types of studies we think about.

HOWARD A. HEIT, MD, FACP, FASAM: I think following on what Marty said, I'd look at it the opposite way is that if I do a point-of-care screening in my office and don't expect it to be positive, that's good news. The point-of-care testing is good for natural opiates, such as codeine and morphine, it won't tell you which one. It's also good to rule out marijuana and cocaine. So to say a negative point-of-care testing can actually be reassuring that at least they're not doing X, Y and Z, as long as you record that in the chart. So just taking 100 degrees opposite.

MATTHEW WIEMAN, MD: How about those other major

issues? When you read the next study, I mean, I would assume this is true, but is there any kind of more direction you might be able to give us on function, quality of life? What do you want to see about that? Are there specific tools you do like? Are there outcomes that you want to see that you're more excited to read about?

JOHN PEPPIN, DO: You can take outcomes that are clinically relevant. So dropping your pain numbers by 20 percent may or may not be statistically relevant, but may not be clinically relevant. So functionality of course is something that everybody harps on. Frankly I think that should be part of any clinical trial. But let's say for this, you can do this very simply. There's a thing called the 6-minute walk, which we've actually gotten a couple of companies to do. It hasn't been validated in chronic pain, but it's been validated in a number of other disease states. And you just make marks on the carpet, you walk 6 minutes, and you write down the distance. And then they can do it again, see if they have improved. It's very simple.

MATTHEW WIEMAN, MD: How about sleep?

MALE SPEAKER: I wanted to go back.

MATTHEW WIEMAN, MD: Yeah, let's go back.

M. CARY REID, MD, PHD: Because of activity and the mobile health, lots of interest in activity looking at these tools to quantify amount of steps per day, amount of time

spent out of the apartment. And moving way beyond the self-report measure, where those data are collected on the outside. And I'm not opposed to the performance-based measures, but I think in conjunction with would be important.

MATTHEW WIEMAN, MD: That's a good point.

STEVEN P. COHEN, MD: The issue with sleep I think is really, really important and there's a very, very high co-prevalence rate. Opioids induce sleep, but they decrease all slow-wave sleep, or stage 3, stage 4, and they decrease REM sleep. And you need slow-wave sleep for regeneration of tissues and healing and immune function. You need REM for sanity, memory formation. There's no question that it's going to affect. So are you going to basically send them for sleep studies? And it's going to decrease. There's no question it's going to decrease all that sleep. Or are you going to use some of these scales? We measure sleep with one, like Athens. I don't think it's the most common. They have a lot of them.

But if they're on it for a long period of time, are they going to be on steady doses? Because when you first take opioids, you increase the amount of time that you sleep, especially with long-acting. But it doesn't mean that it's good sleep. And then when they're on it for a longer period of time, then you have a paradoxical effect. I think

it's just a very difficult thing to deal with sleep. I mean, it would be great if you could. I think if they made those core domain outcome measures, that would be one right now. But it's not because they made them (inaudible).

JOHN PEPPIN, DO: (inaudible) potentially this could be a class effect. Unfortunately the data isn't --

MATTHEW WIEMAN, MD: As you had mentioned, this is the conundrum that we're in: trying to be able to prove some of the uniqueness in the drug.

MALE SPEAKER: It would be very helpful to do it for one particular entity.

MATTHEW WIEMAN, MD: And we don't know the details yet. There's lots of work to be done. And again, we may run into a wall on any one of these.

STEVEN P. COHEN, MD: You have to do psych stuff.

MATTHEW WIEMAN, MD: Psych stuff is the next one I was going to bring up: isolation, depression. Are these things that you want to see on these studies?

STEVEN P. COHEN, MD: But how are they different than any other opiate I guess is what I'm saying.

MATTHEW WIEMAN, MD: We don't know, but again in this case we would hope to find out if there is a hit, and if there isn't, right now we would at least be producing data that other people don't have on certain disease states. I'm not saying that's the way to go. That's why I'm having

to say tear it up. I'm agreeing with all of you on this. There's a struggle to decide which one is the most valuable. Because that's what the real question is with this wall here. And I'll just finish it up, the last pieces are the continuum of care. And I think we really have gone through that pretty in detail, and there's a lot of potential.

So if you looked at all these before I hand it over to Rob, who's going to go over a couple of things that I might have missed. He took some notes about some major topics. If you look at these basic ideas, and you had a set amount of dollars to spend, where would you rank these? High dose, cancer study, other types of disease state studies, which we already talked about we'd hopefully add some interesting endpoints, the continuum of care information.

And then one thing I didn't mention yet was going more into detail on either a separate study or a study that combines cognition and psychomotor. Is there anything there that someone wants to say, "That's my favorite."

NALINI VADIVELU, MBBS, MD, DNB: Can we do a methadone study comparing with the different opioids, where we're looking at patient satisfaction and also nausea and vomiting.

MATTHEW WIEMAN, MD: Okay. So it's more patient-related outcomes it looks like, patient-reported outcomes.

GAVRIL W. PASTERNAK, MD, PHD: It seems to me that

a lot of things you're looking at there, you're going to have a negative effect of the drug. You know, cognitive, psychomotor effects. We know that opiates will work for neuropathic pain, but at very high doses or higher doses, much more likely to have side effects. So I'm not so sure that I would necessarily jump into a study where I know that the drug is going to be a negative and it hasn't been studied before. Why do you want your drug known as the negative? Even if the others have the same effects, your drug is the one that's been actually demonstrated to be, proved to be negative.

MATTHEW WIEMAN, MD: It's definitely part of the risk:benefit analysis of doing these studies.

Randy: One of the reasons why cognitive is up there is the feedback we've received is that relative to the other long-acting opioids, that Opana ER actually has less impact on cognitive impairment. So we're trying to see is there a way to explore does this product actually have less relative cognitive impairment versus MSC or Oxy.

MARTIN D. CHEATLE, PhD: If you can prove that in the psychomotor effects, then it doesn't matter what the disease state is. It separates it.

MATTHEW WIEMAN, MD: That's why these will be sprinkled into the appropriate study.

MALE SPEAKER: If you have someone with cancer who

has difficulty with ambulation because of their chemotherapy, it would be important to have a drug that doesn't complicate that more than another drug.

MATTHEW WIEMAN, MD: Yeah. If you took a geriatric pain patients, OA patients, started them on morphine, started them on Opana ER, followed out their psychomotor, followed out something. You're absolutely right. There is very detailed analysis going on right now which you're a part of, of the risk:benefit analysis of doing this. But this has all been really good feedback.

MALE SPEAKER: It would have to be in opiate-naive patients.

MATTHEW WIEMAN, MD: Sure they may already be --

HOWARD A. HEIT, MD, FACP, FASAM: That's the studies that have been done with driving. They could say that it did affect your reaction time, but they couldn't say anything about cognitive skills, because they didn't have a measurement before let's say addiction was present, before cancer was present, before chronic pain was present, which all affect cognitive development.

MATTHEW WIEMAN, MD: Yeah, it gets very complicated. We'd have to decide what we'd be willing to live with.

MALE SPEAKER: It would have to be very pure.

MATTHEW WIEMAN, MD: Yeah.

HOWARD S. SMITH, MD: Unless it was a cancer crossover, morphine and then over to oxymorphone.

MATTHEW WIEMAN, MD: That's absolutely on the board for discussion.

STEVEN P. COHEN, MD: There was a study in post-herpetic neuralgia that compared amitriptyline to morphine, and it favored morphine, but the p-value was 0.06. So I mean, at least with shorter term follow-up, you don't even have to compare it to another opioid, you could compare it to gabapentin or you could compare to amitriptyline.

MATTHEW WIEMAN, MD: Lots of options.

MALE SPEAKER: But you can see the criticism of that. You're using different classes of drugs, et cetera. It's hard to know.

MALE SPEAKER: The drug class thing, no matter which one of those studies you do you're going to run into that.

MALE SPEAKER: No, but if you're using an opiate, you're using opiates.

MARTIN D. CHEATLE, PhD: But the market share you're trying to increase is in one opiate versus another. So if I prove that this is better than gabapentin, I go --

MALE SPEAKER: Right. We said that's a problem for every single study unless you compare one to another.

MATTHEW WIEMAN, MD: And now I know this is a class

effect, as well, or it's an effect of making someone feel better, and I've already mentioned this before, but is there a way that we could create some interesting endpoints that focus in on the psychiatry of the patient?

GAVRIL W. PASTERNAK, MD, PHD: I still have a problem. It's like trying to fix somebody up with a girl. And you say, "She's not as ugly as the last one." [Laughter] I think going after the negatives, you know, people are just going to remember the negative aspect of it.

MATTHEW WIEMAN, MD: Then you know what? It's totally valid. So then I would ask you, what is your best shot on goal for oxymorphone if you can do one thing this year?

MALE SPEAKER: I have to think about it a little more. But see what things you could do where the oxymorphone would be a positive, not where it's going to be just not as bad as the other one.

JOHN PEPPIN, DO: For example, what if you had the money and were willing to do this, but you did a study on as many opiates as you -- methadone, oxycodone, oxymorphone, and just do five or six. And you look at sleep studies and see if it induces sleep apnea. I mean, that would be very helpful for us as clinicians because maybe one opiate's worse than another. I don't know.

MALE SPEAKER: It will never happen.

MALE SPEAKER: They're all negative.

GAVRIL W. PASTERNAK, MD, PHD: It's sort of like focusing on the wart. In other words, from the marketing perspective, I think focusing on negatives is not the best way to go. But in terms of medicine, I think it would be wonderful to have that information. I was just thinking in terms of from the company perspective.

MATTHEW WIEMAN, MD: Well, thank you. I really appreciate it. I think we had a really good discussion. We'll wrap up a couple of points with Rob, and then he's going to hand it back over to me just to finish up. But I'm going to be touching back again with all of you as well to talk about each of these and flesh some of them out if you can. And you can see the issue we have here is we're trying to find some meaningful data to move forward with for this life cycle of the product. Thank you.

[FILE 6]

Closing Statements

ROB GATLEY: I'm just going to touch on some points aside from those ones that were the specific goals before we had the meeting. Some other things that came up during the discussion that I think are also of value pursuing. I know the first session we had on best practices and education, it was highlighted that the culture of practice is an issue, of an inertia towards change, reluctance to implement things

that are brought up through education and following mentors who might not be following a good pattern of practice.

So I think one of the things that came out of that is the importance of novel ways of implementing education. We brought up apps, electronic medical records. One of the things that a pharmaceutical company could do is a program to link up practitioners with mentors with access to comment and to possibly sessions at meetings, to link up practitioners with someone who does have a good standard of care. I think an important thing that came out of that session was the idea that if you're getting into the electronic media, you've also got an instant source of data. So I think that's something we should look at, is ways to develop those ideas into a source of data and some ongoing study.

I also was thinking about this after we had that discussion with the whole idea of your following your mentor who you respect as a clinician, you're not going to question him, but we're in this age of electronic media. It brought me to mind of the Arab Spring. If you're going on rounds with your smart phone, are you going to maybe say, "Well, Gavril Pasternak says this."

GAVRIL W. PASTERNAK, MD, PhD: Oh, they won't do that.

ROB GATLEY: I think that's an area to explore.

[Background Conversation]

MATTHEW WIEMAN, MD: Be careful what you say.

ROB GATLEY: So I think maybe a way to think in that area of educational issues, you would say would be the most important, as a priority to work in that area: apps, CMR, online education. What would be a priority to head off on for an initiative?

JOHN PEPPIN, DO: We did a program with Pearl Schwartz, what's her group? Creative Educational --

HOWARD A. HEIT, MD, FACP, FASAM: It was case-based.

JOHN PEPPIN, DO: It was case-based. And they actually had an actor who played the role of a patient. It was really quite good.

CHRIS HERNDON, PharmD: That was fun.

MALE SPEAKER: And Chris did that, that's right. You did that, too. And we really had a good time. But they had a booth on a couple of these where you would go in and sit down, and the doc and the patient would interact and ask questions. And I think they had some data going out about six months.

MALE SPEAKER: You entered a sort of like hallway, and there were posters. And you stood in front of the posters and used your --

MALE SPEAKER: I remember that.

[Crosstalk]

MALE SPEAKER: -- what do you call it? The video hand-held, what's the hand-held device they used?

MALE SPEAKER: (inaudible) response system?

MALE SPEAKER: No, the device. One of us would speak about the poster, and you'd go through eight posters. It took 20 minutes. Then you went into an examining room in which there were certain questions you would ask. Like, "I want to do a urine drug test." And the actors would say, "Why? Do you think I'm an addict?" And how to respond to certain things. "Why do I have this? It's my Constitutional right. I don't have to do this." Or that the urine test came back inappropriately positive, how did you react. It was like case-based learning, and it was very well-received.

MALE SPEAKER: And they actually looked at I think about six months as far as the effect.

MALE SPEAKER: The retention there was great.

MALE SPEAKER: The retention was really good.

MALE SPEAKER: But it was very time intensive.

MALE SPEAKER: And expensive.

MALE SPEAKER: And expensive.

MATTHEW WIEMAN, MD: That reminds me of something, to expand upon that. It reminds me of doing the simulator training in residency. You know, whatever your simulation was. Most of us it was going into the OR and there was an

airway fire or some major disaster. And everyone's watching you from above.

Again, time intensive is the issue. Because we know that we have this type of like in medical school training, there already is the ob/gyn, get over the ob/gyn nervousness, examining that patient. You get tested basically on seeing a patient. But should pain be, since it's very unique, could we try to get that devoted to? And potentially again, actors and/or a type of a simulation where it's more interesting.

JOHN PEPPIN, DO: You might be able to do a web-based thing or something. There's ways to do I think that wouldn't be as expensive.

ROB GATLEY: That would reduce costs. And also there's the potential with that kind of thing you can go through electronically, answer the questions, see the electronic patient, and have someone online available for chat some specialists who are doing it in their time to be available for those to give you that feedback.

ROB GATLEY, MD: It would be a hell of a lot cheaper, and plus they could do it on their own schedule.

MATTHEW WIEMAN, MD: Yeah, you wouldn't be taking anything out of their either school curriculum or their work. They could do it after.

GAVRIL W. PASTERNAK, MD, PHD: Do you worry about

the number of these programs that people are getting hit with these days, and whether you're going to make an input? I mean, I probably get about 20 of these a week from various different organizations, from neurology and cardiology sending them to me, God knows why. I'm just wondering as the web becomes very much used, at what point do people just desensitize? I mean, 15 years ago I answered every email. Now half of them get thrown away without even looking past the title. I'm just curious how you would make it so people would actually pay attention to yours as opposed to someone else's.

ROB GATLEY: Probably the most effective way is coupling it with real-life mentoring. If your attending suggests that you go to this website, or somebody you refer to for pain consults recommends it.

CHRIS HERNDON, PHARMD: Or make it CME.

ROB GATLEY: I guess if your drug rep recommends it, as well. But then you get into the whole question of that wouldn't be CME if it's linked to the pharmaceutical company as the source.

CHRIS HERNDON, PHARMD: Are you talking about training people already in practice or postgrads?

ROB GATLEY: It could be for either. The event at APS was for clinicians in practice. But it's a good model.

MALE SPEAKER: Pain Paradox.

MALE SPEAKER: Pain Paradox, yeah. That's right.

JOHN PEPPIN, DO: One of the ideas that I had discussed, we've just never been able to pull together because of funding but would be, let's just say we're going to use residents, maybe family practice and internal medicine residents. And you make it competitive.

So the director of a program recommends someone. And then they go to a meeting. Say you pick 30, 40, I don't know, however many, and they go to a meeting. And it's very interactive, case-based. You have some of the mentors there, folks like us would be there, and we interact with them. And then over the year, they would have to do certain things on the web and interactive. Maybe you have a meeting at the end. And that kind of input over a year I think might actually make a difference. It's a small group, but still. It's a start.

MATTHEW WIEMAN, MD: Well, that's it. We all agree it's not working right now, and there's got to be more of it. And it's got to be in a different format. So we're going to have to make it creative enough and interesting enough so that we get that retention, and then you also get even the initial, "I'm going to answer the email," or "I'm going to buy into this as an idea."

GAVRIL W. PASTERNAK, MD, PHD: You were talking about these programs at the APS. That's bringing coals to

Newcastle, isn't it? I mean, they're the people who are already interested in pain, and the people that you really need to educate are the people -- I mean, the hardest thing is when the people don't realize how ignorant they are. And so what you really should be focusing on to me would be the family practice guys, pediatricians who have a lot of difficulty with pediatric pain. It's very difficult to evaluate and people are very reluctant to treat.

MATTHEW WIEMAN, MD: Yes, so some of the folks that are referring to you, just messed cases already. And those are the folks who would get the most out of this. And we are currently dealing with just restrictions on who we can actually proactively reach out to because they don't allow us to expand the long-acting market. So ironically, the folks that need the data the most, the pharmaceutical companies are not allowed to get too close to.

MALE SPEAKER: But if you're educating them about pain.

MATTHEW WIEMAN, MD: Yes.

MALE SPEAKER: As opposed to educating them about oxymorphone. I mean, that would be an extraordinary service.

MATTHEW WIEMAN, MD: This goes back to the original comment, I forget who made it, but at the beginning the suggestion was to even potentially have whoever the person comes up and speaks to you is focused more on the education,

less on -- if we don't have an enormous amount to say, this is what I heard anyway, about one particular thing, you may get a lot more credibility by walking in the door and saying, "Let's talk about pain for a little bit."

ROB GATLEY: I think an important concept that came up a lot when we were talking about education best practices is, is this going to change things. Is this program, that thing, going to actually change practice? So one thing with the apps, the EMR, with the idea of something web-based is if you can gather data, and six months down the line poll these same people who went in before and say, "Has it changed your practice?"

So maybe, Gav, what were you saying? How do you sell this as being a better source of information than all 20 others out there. If it was perhaps started in an academic environment, where you do the program, you follow up in six months, did it actually make a change? If it has a validation as being effective.

GAVRIL W. PASTERNAK, MD, PHD: There are a lot of academic places and people that would be very interested in this kind of educational approach. And with a nonrestricted grant, people I think would be very, very happy to set these things up for you.

MALE SPEAKER: Another thing is medical students, often all they use is their palms. Remember the big books

you used to carry in your pocket? It's all gone. They just kind of look up what the disease state is and what the drugs are. It would be very easy just to sort of lap in something that has to do with pain education.

ROB GATLEY: I think something that would draw people back to it, too, is through gathering the data and following up, you make that person an individual. They haven't just visited a website anonymously, but you're following up and measuring what's happened in their own practice.

JOHN PEPPIN, DO: I don't think we ask them, "Has this changed your practice." I think we measure that in some way. So maybe they have to give five cases or maybe we have to ask them questions about some cases or something.

MATTHEW WIEMAN, MD: Anyone who comes on, say someone who rotates through, whatever number comes in for the next rotation for the pain practice, the pain service, they're rotating through perhaps, give that one crowd a set of those case studies and have them do it again at the end. Like you said, some sort of measurement with an academic group that you're following, there's an incentive for them to try, they have to do this, to see if it works.

PATRICIA BRUCKENTHAL, PhD, ANP-C: One thing I did for simulating patients, we started previewing that our students love is the digitalized patients. So we have a case

that teaches health assessment through all the systems, and her memory is unbelievable. So you can type in your assessment questions, and then the digitalized patient verbally answers you. And check, she has a mother who's sitting in the room. You can ask the mother to leave, and ask her some other questions. I don't know how much that costs, but it's a really engaging method of learning.

ROB GATLEY: It actually costs less than doing it live time at a conference.

PATRICIA BRUCKENTHAL, PhD, ANP-C: But everybody loves to access it. The Digital Age.

MALE SPEAKER: That resident thing, you can call it the Pasternak Award, and you have a little bronze, just a moustache, just on the top.

ROB GATLEY: One other area I think we need to get back to is just the whole thing with different formulations and with the oxymorphone molecule itself. Availability, access, familiarity were things that came up as themes again and again. We're not going to use it if it's not available. We're not using it. We're not going to ask for it. So I think there's a need for initiatives to get out data from whatever centers are using IV oxymorphone or who are using IR as a first-line if there's something published within there's a ground to try using it or advocate for it to be covered. And then that also establishes experience. So those

are initiatives, getting out data of people who are actually using these things.

CHRIS HERNDON, PHARMD: One quick barrier that I find a lot when I actually do write for one of the TRICARE patients for this stuff, it is terrible for them to find a pharmacy that actually has it. And so if you guys could like maybe negotiate with one of the large chains to stock at least one bottle of the common strengths or something. I mean, it takes hours to dig through the local places to find who has them. I don't know why they're so reluctant to stock it. But it really is a barrier for me.

MATTHEW WIEMAN, MD: Yeah, we found that to be very true and very regional. But it's a big issue, and we're certainly working on different angles for our pharmacy connection.

Well, I think we're pretty much at the end here. Thanks, Rob, for finalizing all this. Howard, would you like to just say a final word or two. Thanks for all your help.

HOWARD S. SMITH, MD: Thank you, everybody, for coming. It was a very lively discussion. Does anybody have any last words or advice for Endo as far as a particular study that would be important, like one thing that they could do or two things that they could do in terms of education, clinical study, review article that would be important?

MATTHEW WIEMAN, MD: I think we've had a lot of discussion today. It's a little bit hard. But this is just the beginning. So we now have all met here to open the discussion. We'll be obviously coming back with a lot of information and kind of summaries on what we did discuss. I'll be reaching out to each one of you to discuss some of the specific areas that you expressed interest in and to ask you some more questions. So I think there's a lot of opportunity to work together I the next year. And again, as you come up with these ideas on your plane or train or car ride home, take a second and write it down so when I reach out next time, we'll continue our conversation.

MALE SPEAKER: Thank you.

MATTHEW WIEMAN, MD: Thank you. Thanks, everybody. Safe travels. [Applause]